# PEDIATRIC HYPERTENSION: UPDATE

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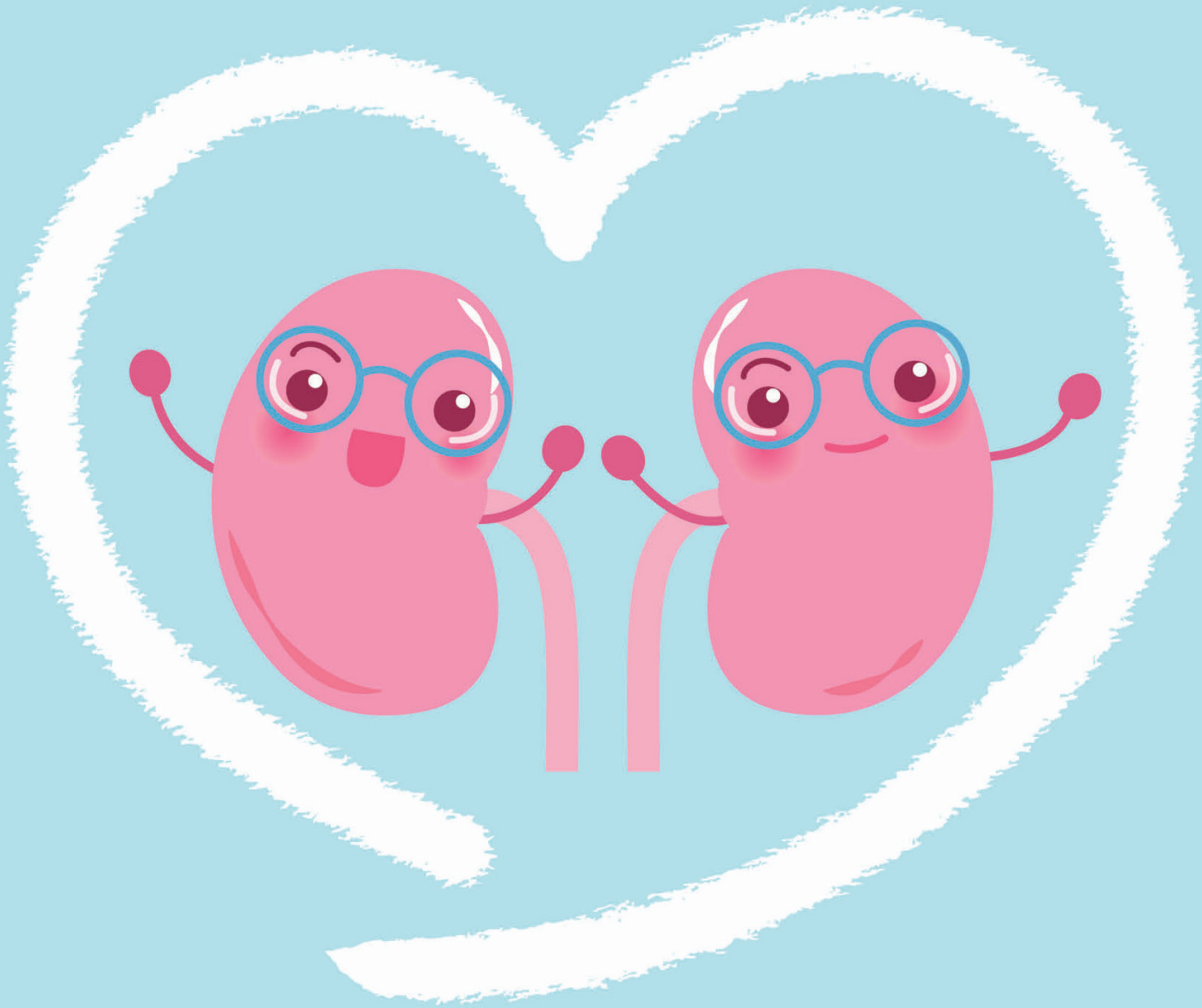

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# PEDIATRIC HYPERTENSION: UPDATE

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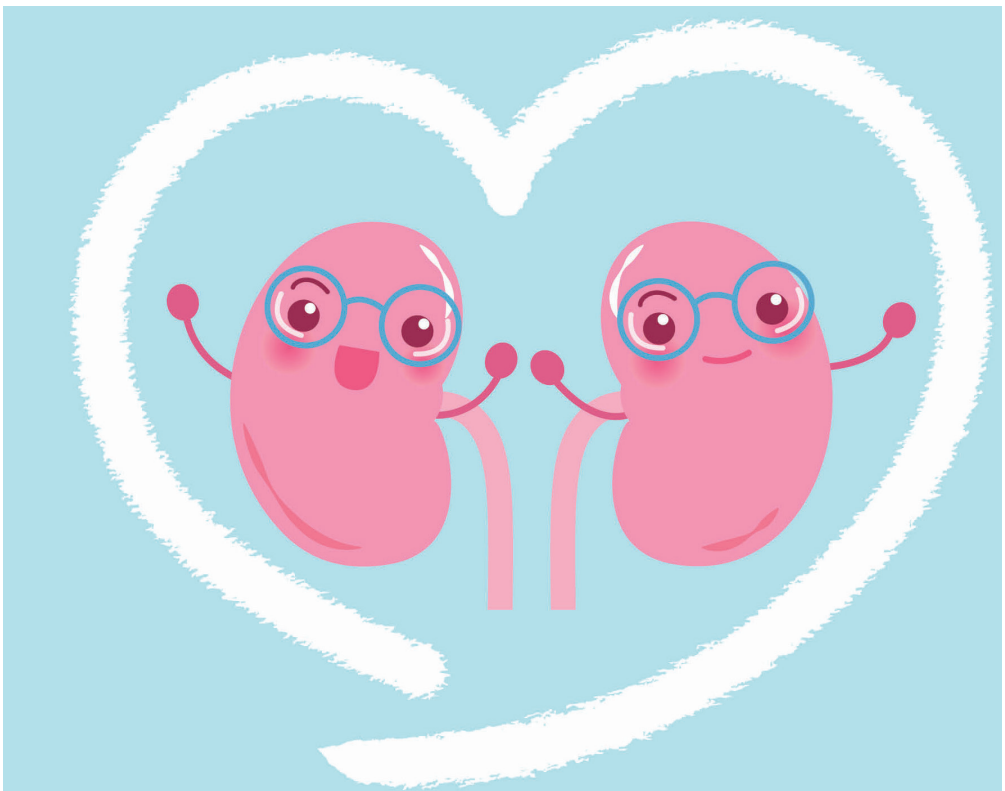

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EDITORIAL
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# Editorial: Pediatric Hypertension: Update

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**Keywords: LVH, obesity, microbiome, genetic programming, pheochromocytoma, paraganglioma, developmental origins, kidney transplant**

## Editorial on the Research Topic

## Pediatric Hypertension: Update

Hypertension in children and adolescents remains a significant health care concern. Epidemiological studies now report that the prevalence of pediatric hypertension ranges from 3% in the general population to up to 25% in obese children. Historically, pediatric hypertension was considered a secondary phenomenon until proven otherwise. However, more recent evidence describes primary hypertension as being more likely than secondary hypertension among children referred to subspecialty care for evaluation of elevated BP in communities where obesity is prevalent. This shift highlights the early relationship between obesity and learned behaviors such as sedentary lifestyle and increased salt/caloric intake with blood pressure.

In this special pediatric hypertension series, we have assembled contributions from global experts in childhood hypertension to provide the reader with a comprehensive and current update on the varied aspects of hypertension diagnosis, secondary etiologies, and cardiovascular co-morbidities. We were fortunate to enlist a prominent group of 22 authors to contribute a wide range of articles. In total, 10 papers have been included (Lewis et al.; Peterson and Miyashita; Al Khodor et al.; Bholah and Bunchman; Woroniecki et al.; Fernandez; Ahn and Gupta; Gurusinghe et al.; Charnaya and Moudgil; Brady).

We introduced the topic of Pediatric Hypertension with a review article highlighting current methodologies and recommendations for hypertension screening in children and adolescents (Lewis et al.). The article by Michaela Lewis, Ibrahim Shatat, and Shannon Phillips walks readers through key issues contributing to both the inaccurate measurement of blood pressure and the misclassification of HTN among children and presents strategies to address these issues. As the authors point out, although national guidelines for the diagnosis and management of pediatric HTN have been available for nearly 40 years, knowledge and recognition of the problem by clinicians remains poor due to a host of influencing factors. They bring to the reader's attention a host of potential exposures known to affect BP, such as recent use of tobacco products, e-cigarettes, consumption of a sodium-rich or high caffeine diet, as well as multiple over-the-counter, herbal, and prescription medications. The authors provided the readers with a comparison between

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different available measurement devices [Table 1 in (Lewis et al.)]. Last year and after this review (Lewis et al.), the AAP clinical practice guideline for screening and management of high blood pressure in children and adolescents (1) were published. In the new guidelines, the AAP recommends limiting screening BP measurements to preventive care visits for children without risk factors (while continuing to recommend BP screening at all visits for those at increased CVD risk), introduced updated BP tables based solely on normal-weight children, and a simplified BP classification in adolescents ≥13 years of age.

The new guidelines expanded the role for ambulatory BP monitoring (ABPM) in the diagnosis and management of pediatric hypertension. Caitlin Peterson and Yosuke Miyashita contributed an article (Peterson and Miyashita) to this collection emphasizing that 24-h ABPM should be considered standard of care in pediatric patients. In their manuscript, the authors highlight how ABP is superior to clinic BP in evaluating elevated BP and in diagnosis and classification of HTN. In Table 1 of their manuscript, they summarize pediatric studies that examined the association between TOD and ABPM, while in Table 2 they explore potential future clinical applications of 24-h ABPM.

In two of the best written reviews in the field, Sun-Young Ahn and Charu Gupta reviewed for the readers the topic of genetic programming of hypertension (Ahn and Gupta). Table 1 in this review elegantly summarizes monogenic forms of hypertension, while the text discusses methodologies employed in genetic studies of essential HTN, mechanisms for epigenetic modulation of essential HTN, pharmacogenomics and HTN, and recent advances in genetic studies of essential HTN in the pediatric population. Complementing this review, Shari Gurusinghe, Anita Tambay, and Christine Sethna reviewed the developmental origins of hypertension and the role of nephron endowment (Gurusinghe et al.). The authors guide the readers through one of the most intriguing concepts in pediatric nephrology, that is, how the in utero environment may increase the risk of both hypertension and chronic kidney disease. In Figure 2 of their manuscript, the authors propose a flow chart linking low nephron number to hypertension. Furthermore, the authors discuss the impact of ethnicity and postnatal modifiers on nephron numbers.

Tammy Brady contributed a review that focused on the unique aspects of hypertension evaluation and management in the child with comorbid obesity (Brady). Charnaya and Moudgil reviewed the etiology of post-transplant hypertension (Charnaya and Moudgil); they pointed out that HTN is both a risk factor for graft loss and a consequence of multiple transplant related factors including: donor characteristics, recipient factors, medications, and lifestyle attributes similar to those associated with hypertension in the general population. The authors further discuss other useful techniques to assess CVD in this at risk population.

In a comprehensive review of a potentially curable cause of secondary hypertension in pediatric patients, pheochromocytoma (PCC) and paraganglioma (PGL), Bholah and Bunchman point out that these conditions are inherited in as much as 80% of pediatric cases, and that all patients with mutations should be followed closely given the risk of recurrence and malignancy. In figure 1 of their review, the authors reproduced with permission from Lenders et al. (2) a proposed algorithm for genetic testing of patients with PCC or PGL based on clinical characteristics, biochemical phenotype, and tumor pathology. They also outline the pre-, intra- and postoperative management of these challenging tumors as well as follow up.

Woroniecki and colleagues discussed in their review one of the intermediate outcomes resulting from pediatric hypertension: left ventricular hypertrophy (LVH). The review covers the topic from epidemiology to current definitions, clinically relevant methods of left ventricular mass (LVM) measurements (including new methodologies such as cardiac magnetic resonance) and normalization. It also covers clinical management of LVH and how to best achieve regression of LVH in children with HTN (Woroniecki et al.). This review was followed by a commentary by Fernandez in which the author points out that the PESESCAD-HTA study found diastolic abnormalities even in prehypertensive adolescents without LVH, which underlines additional adverse effects of elevated BP and hypertension on the heart.

In the last review of this article collection on pediatric hypertension, Souhaila Al Khodor, Bernd Reichert and Ibrahim Shatat introduce the readers to the relatively new area of investigation in the field of hypertension, posing an interesting question: Can Microbes Regulate Our Blood Pressure? In Figure 2 of their review (Al Khodor et al.), the authors summarize the current hypotheses linking dysbiosis and blood pressure regulation. They point out that while the field is still in its infancy, researchers have started to examine changes in blood pressure when the microbiome is manipulated by dietary and lifestyle changes aiming to achieve a more balanced microbiome.

Our overarching goal of this compilation was to provide the reader with an up-to-date review of pediatric hypertension and to stimulate interest among academic and practicing physicians and scientists on this important topic. With longitudinal studies clearly demonstrating that blood pressure and hypertension in childhood tracks into adulthood, we hope these comprehensive reviews spur more research focused on decreasing the growing burden of hypertension and cardiovascular disease worldwide.

## AUTHOR CONTRIBUTIONS

IS wrote and reviewed the editorial. TB contributed to review process and editing.

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MINI REVIEW
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# Screening for Hypertension in Children and Adolescents: Methodology and Current Practice Recommendations

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Hypertension (HTN) requires urgent, uniform, and consistent attention across all frontiers of pediatric health care not only because of established links between the onset of HTN during one's youth and its sustenance throughout adulthood but also because of the sequelae associated with the disease's trajectory, such as cardiovascular disease, end organ damage, and decreased quality of life. Although national guidelines for the diagnosis and management of pediatric HTN have been available for nearly 40 years, knowledge and recognition of the problem by clinicians remain poor due to a host of influencing factors. The purpose of this article is to explicate key issues contributing to the inaccurate measurement of blood pressure and misclassification of HTN among children and to present strategies to address these issues.

**Keywords: blood pressure measurement, hypertension, ambulatory monitoring, children, oscillometric**

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## INTRODUCTION

Hypertension (HTN) requires urgent, uniform, and consistent attention across all frontiers of pediatric health care not only because of established links between the onset of HTN during one's youth and its sustenance throughout adulthood but also because of the sequelae associated with the disease's trajectory, such as cardiovascular disease (CVD), end organ damage, and decreased quality of life.

Between 2011 and 2014, the prevalence of HTN among children and adolescents aged 8–17 years was approximately 2.2% (1), a number similar to other chronic childhood illnesses that garner more attention, such as asthma (9%), autism (1%), or epilepsy (1%) (2). Up to 30% of newly diagnosed hypertensive children demonstrate significant target organ damage, particularly left ventricular hypertrophy (2). Pediatric HTN is an issue attracting attention on a national level, as the reduction of the proportion of children with HTN is an active objective of the Healthy People 2020 movement (1).

Although national guidelines for the diagnosis and management of pediatric HTN have been available for nearly 40 years, knowledge and recognition of the problem by clinicians remain poor due to a host of influencing factors (3). Faulty blood pressure (BP) testing can lead to misdiagnosis and unnecessary treatment, so proper BP measurement methods are essential. To obtain accurate BP measurements, clinicians must consider the type of equipment to be used, training personnel on proper technique, the environment in which measurement is conducted, classification of BP according to recommendations, and assessment for factors that could affect BP. The purpose of this paper is to provide an overview of practice recommendations, including a discussion of factors that may impact a provider's ability to appropriately assess pediatric patients for HTN.

## PRACTICE RECOMMENDATIONS

The United States Preventive Services Task Force states that the current evidence is insufficient to assess the balance of benefits and harms of screening for primary HTN in asymptomatic children and adolescents to prevent subsequent CVD in childhood or adulthood (4). The lack of compelling evidence to universally screen healthy children was also highlighted in a review by Chiolero and colleagues (5). However, given the implications of HTN and CVD in adulthood, a lifespan approach of early screening has been advocated by the National Heart, Lung, and Blood Institute (NHLBI) (6) and the American Heart Association (AHA) (7).

The AHA (7), NHLBI (6, 8), and American Association of Pediatrics (9) recommend that children over 3 years and under 18 years receive a BP measurement at least annually, and once during every health-care episode. Children under 3 years should have their BP measured in special circumstances such as a history of being very low birth weight, history of recurrent urinary tract infections, and congenital heart disease.

### Device Selection

When selecting a device, clinicians must consider the necessary equipment, advantages, and disadvantages associated with each option. The most commonly used devices are the mercury sphygmomanometer, the aneroid sphygmomanometer, the office oscillometric device (single and serial measure), and the ambulatory blood pressure monitor (ABPM). **Table 1** outlines key considerations for each device.

The gold standard is auscultation using a mercury sphygmomanometer; NHLBI BP classification tables are based on auscultatory measurements (6, 7). Since use of an appropriately sized cuff is critical for accurate measurement, the AHA advises clinicians have the following cuff sizes on hand: newborn/premature infant (4 cm × 8 cm), infant (6 cm × 12 cm), older child (9 cm × 18 cm), standard adult, large adult, and thigh for leg measurement or for children with large arms (7). The bladder width should be at least 40% of the patient's arm circumference midway between the olecranon and acromion processes and should cover 80–100% of the circumference of the arm (6, 7).

While the mercury sphygmomanometer is considered the gold standard, concerns have arisen about mercury contamination leading to this device being banned in some locations (7). The aneroid sphygmomanometer is a more environmentally friendly alternative that uses metal bellows and levers to register pressure. However, the aneroid sphygmomanometer tends to be less accurate than the mercury sphygmomanometer and requires regular calibration. Wall-mounted aneroid units are less likely to be dropped or subject to trauma and are more accurate than mobile devices (10).

**TABLE 1 | Blood pressure measurement device selection.**

| Device | Equipment | Advantages | Disadvantages and other considerations |
|---|---|---|---|
| Mercury sphygmomanometer | • Mercury column<br>• Stethoscope<br>• Appropriately sized cuff with bladder and inflation bulb | • Considered the "gold standard"<br>• Directly comparable to classification tables normative data | • Environmental concerns about mercury contamination<br>• Potential for error and bias |
| Aneroid sphygmomanometer | • Lever and bellow aneroid unit<br>• Stethoscope<br>• Appropriately sized cuff with bladder and inflation bulb | • Ecologically friendly alternative to mercury sphygmomanometer | • Tends to be less accurate than mercury<br>• Susceptible to reading errors resulting from trauma to the unit<br>• Requires regular calibration<br>• Potential for error and bias |
| Office oscillometric (single measure) | • Automated unit validated in pediatric populations<br>• Appropriately sized cuff | • Easier to use than sphygmomanometer<br>• Ecologically friendly<br>• Less susceptible to error and bias<br>• Easier to use in situations when auscultation is challenging<br>• Beneficial in situations when frequent measurement is necessary<br>• Cuff placement less critical | • Wide variation in devices<br>• Device should be validated in children prior to use<br>• Susceptible to inaccurate readings in certain situations<br>• Susceptible to movement artifact |
| Office oscillometric (serial measure) | • Automated unit validated in pediatric populations<br>• Appropriately sized cuff | • Can assist with accurate diagnosis of hypertension (HTN)<br>• Reduces effect of white-coat HTN and masked HTN<br>• Cost-effective alternative to ambulatory blood pressure monitor | • Few units validated in pediatric populations |
| Ambulatory | • Automated unit for home use validated in pediatric populations<br>• Unit able to store and download data<br>• Appropriately sized cuff | • Can assist with accurate diagnosis of HTN<br>• Reduces effect of white-coat HTN and masked HTN<br>• Can identify non-dipping BP pattern<br>• Can monitor BP patterns over time | • May not be well tolerated in children<br>• Requires family training and cooperation<br>• Susceptible to misreporting<br>• Normative values differ by sex and race<br>• Requires consultation to pediatric HTN specialist<br>• Equipment and analysis can be costly |

To measure BP using either the mercury or aneroid sphygmomanometer, the clinician inflates a cuff to a pressure greater than the SBP, thus occluding the brachial artery, then gradually deflates the cuff to auscultate sounds using a stethoscope placed at the artery below the cuff. A disadvantage of both options is the potential for observer error, such as differences in training, terminal digit preference, and expectation bias due to knowledge of previous readings (5).

Oscillometric (automated) BP measurement devices have rapidly replaced sphygmomanometers in clinical practice. These devices are more ecologically friendly, easier to use, and eliminate potential sources of bias. Oscillometric devices are also beneficial in situations in which auscultation is challenging, such as with newborns and young infants, where device utilization requires tolerance of excessive motion, and in intensive care settings when repeated measurements are required (7, 11). However, there is wide variation in devices, arterial stiffness and wide pulse pressure can lead to inaccurate readings, and measurement is susceptible to movement artifact.

When selecting an oscillometric device, clinicians should seek instruments that have been validated in the pediatric population (6, 12). The Association for the Advancement of Medical Instrumentation and the British Hypertension Society each developed established protocols for validation, and more recently, the European Society of Hypertension Working Group on Blood Pressure Monitoring developed an International Protocol to validate BP measurement devices (7, 13). To assist clinicians in identifying devices that have been validated and recommended, the dabl Educational established a not-for-profit, foundation-funded website to provide up-to-date validation information on BP measurement devices[1] (14). Clinicians may consult these tables to determine which devices are recommended for use in children.

Serial-measure oscillometric devices are designed to obtain a series of BP measurements at intervals of 1 min or more with the patient seated alone in a quiet room in the office setting. The number of serial measurements varies by device, typically three to six, and an average is calculated. In adults, no significant difference has been found between BP classification using serial measurement technique versus 24-h ABPM. The serial measure oscillometric device, such as the BpTru, can substantially reduce the effect of white coat HTN and masked HTN and can be a cost-efficient alternative to ABPM (15–17). The BpTru has been validated in children aged 3–18 years (18).

In some cases, ABPM is warranted to obtain a more accurate representation of the BP. With this method, BP is measured repeatedly, usually over a 24-h period, and the measurements are stored and downloaded (6, 7). ABPM is indicated when white coat HTN is suspected, to identify a non-dipping pressure pattern, to monitor drug effects (6, 7), and in situations when it is necessary to monitor BP patterns, such as chronic kidney disease, autonomic dysfunction (6), target-organ damage, and low birth weight (12).

[1] http://www.dableducational.org/welcome.html.

Various ABPMs are available, but few have been formally validated in children (11). Beyond ensuring validation of a device, clinicians should identify a monitor that is lightweight, able to tolerate movement, and has pediatric cuffs. Software should be programmable to measure every 15–20 min over 24-h period, and preferably, can provide a report with pediatric reference data (19). ABPM can be conducted with a wide age range of children (20), but may not be well tolerated in all children, requires family training and cooperation, is susceptible to misreporting (12), and equipment and monitoring procedures are costly. Further, normative values differ by sex, height, and race (21, 22).

## Care of Equipment

Equipment must be properly maintained to ensure accurate measurement. Hardware should be cleaned with disinfecting wipes, and ABPM cuff covers should be washed between patients (11). The column of mercury sphygmomanometers should be clean, should rise and fall freely, and the upper curve of the meniscus should rest at 0 mmHg. Aneroid and other non-mercury sphygmomanometers should be calibrated semiannually by connecting the manometer to mercury column or electronic testing device. The needle should rest at 0 mmHg and should read within 4 mmHg of the mercury sphygmomanometer when inflated to 100 and 200 mmHg (6, 7). Since various automated devices are available on the market, calibration should occur according to the manufacturer's recommendations (11).

## Performance Considerations

The use of proper technique when obtaining BP readings is vital in terms of obtaining an accurate measurement and essential in reducing procedure variability. When possible, the patient should be seated with the antecubital fossa supported at heart level. The patient's feet should be on the floor, not dangling from an exam table. Clinicians should remove clothing that covers the location of the cuff. The patient's legs should be uncrossed, with the back and arm supported (7). A cuff placed over clothing can cause a 5–50 mmHg discrepancy in SBP, an unsupported back can cause a 6–10 mmHg discrepancy in SBP, and sitting with the arm unsupported can cause a 1–7 mmHg in SBP and a 5–11 mmHg discrepancy in DBP (23).

In addition to proper positioning, the patient should be in a quiet environment. The clinician should avoid overinflating the cuff, since an overly tight cuff can cause upset in young children. Avoid talking during measurement (7), since talking and active listening can cause a 10-mmHg discrepancy in SBP and DBP (23).

Using the appropriate cuff size is another critical factor, since a too-small cuff can lead to false high readings and a too-large cuff can lead to false low readings (6). A too-small cuff can cause a discrepancy of 10 mmHg in SBP and 2–8 mmHg in DBP (23). Standard cuff placement is the upper arm; the right arm is the preferred site for repeated measures to maintain consistency and for accurate comparison to standards (6). In some circumstances, such as arm fracture or in the case of acute illness, it may be necessary to measure in an alternate site or position. It is important to note that pressures vary by location and position.

## BP Classification

Accurate BP classification requires assessment of the patient's age, sex, and height (7). The clinician first determines the patient's height percentile using Centers for Disease Control and Prevention growth charts, then the clinician refers to the NHLBI (6) standardized BP classification tables to categorize the BP as normotensive, prehypertensive, or hypertensive. The AHA and the NHLBI recommend the patient's BP be measured and recorded at least twice at each occasion, and the average of SBP and DBP be recorded (6, 7). However, Becton and colleagues (24) conducted an evaluation of NHANES data and found that in greater than 90% of adolescents aged 13–18 years, the BP classification remained the same in repeat sequential measurements.

Once the BP is plotted on the appropriate table for age, sex, and height, the percentile ranking is assessed. A BP that falls below the 90th percentile is considered normotensive, while a BP that falls between the 90th and 95th percentile is classified as prehypertension. Further, adolescents with a BP greater than 120/80 should also be considered prehypertensive. Patients with a BP that falls into the prehypertensive range should be reassessed and evaluated for other risk factors (6). A BP that, on repeated assessments, consistently falls equal to or greater than the 95th percentile for age, sex, and height is classified as hypertensive (6, 7). If a BP falls between the 95th percentile and the 99th percentile plus 5 mmHg, the measurement should be repeated on two additional occasions to confirm the classification. However, if the BP is greater than the 99th percentile plus 5 mmHg, the patient should be promptly referred to a specialist for evaluation (6).

Before diagnosing a patient as hypertensive, the elevated BP should be confirmed on repeat visits, as BP measurement is more accurate if averaged over weeks or months rather than at a single visit (6, 7). An exception for this recommendation is when a patient appears symptomatic or has a profoundly elevated BP, in which case the patient should be promptly referred for further evaluation.

Pediatric HTN experts have developed and validated quick reference tables that are easier to use in the busy clinic setting than the complex NHLBI standardized BP classification tables. One example is "A Pocket Guide to Blood Pressure Measurement in Children" developed by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (25). This reference guide is published online by the NHLBI[2] and offers tips on measurement, classification, and interpretation, and a simplified table by age and height.

[2]https://www.nhlbi.nih.gov/files/docs/bp_child_pocket.pdf.

## Other Special Considerations

Clinicians must also assess for factors that could affect BP, such as routine or intermittent medication use, recent use of tobacco products, and consumption of a sodium-rich or high caffeine diet. Multiple over-the-counter, herbal, and prescription medications have the potential to elevate BP, including decongestants, ephedra, ginkgo, ginseng, senna, St. John's wort, and oral contraceptives. Clinicians should also consider whether the patient is being treated for ADHD, since some medications prescribed for this condition may elevate BP. It is also important to assess for use of illegal substances such as anabolic steroids, amphetamines, and cocaine, all of which can affect BP (26).

Use of tobacco products can cause masked HTN (7), and smoking within 30 min of BP measurement can cause a 6–20 mmHg discrepancy in SBP (23). Clinicians should ask questions directed at determining recent tobacco use, but should also inquire about sustained tobacco use since this can cause arterial changes that may affect BP. Smoking in the home, by parents or other residents, should also be assessed, because secondhand smoke can increase BP (27). Clinicians should also consider e-cigarette use, which can increase the DBP; e-cigarette use tripled among middle and high school students from 2013 to 2014 (28).

Finally, clinicians should consider the effect of dietary habits and sleep habits when assessing BP. Increased consumption of processed foods and those high in sodium, and poor sleep are associated with an elevated SBP (12), and caffeine use has been associated with masked HTN (7).

## CONCLUSION

Given the implications of CVD in adulthood, a lifespan approach of early screening for HTN in children is essential in reducing the mortality and morbidity associated with vascular compromise. While this article provides an overview of practice recommendations, current guidelines are actively being revised and updated. Adherence to recommended pediatric HTN guidelines through the use of accurate screening measures and practices and remaining abreast of practice guideline updates is the first step down the path of healing.

## AUTHOR CONTRIBUTIONS

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

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REVIEW
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# The Use of Ambulatory Blood Pressure Monitoring As Standard of Care in Pediatrics

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Hypertension (HTN) is a significant global health problem, responsible for 7.5 million deaths each year worldwide. The prevalence of HTN is increasing in the pediatric population likely attributed to the increase in childhood obesity. Recent work has also shown that blood pressure (BP) tends to track from childhood to adulthood including BP-related target organ damage. In the last 25–30 years, pediatric use of ambulatory blood pressure monitoring (ABPM) has been expanding mainly in the setting of initial elevated BP measurement evaluation, HTN therapy efficacy follow-up, and renal disease. However, there are many clinical areas where ABPM could potentially be used but is currently underutilized. This review summarizes the current knowledge and the uses of pediatric ABPM and explores clinical areas where it can be very useful both to detect HTN and its longitudinal follow-up. And thus, ABPM could serve as a critical tool to potentially prevent early cardiovascular mortality and morbidity in wide variety of populations. With solid data to support ABPM's superiority over clinic BP measurements and these clinical areas for its expansion, ABPM should now be part of standard of care in BP evaluation and management in pediatrics.

**Keywords: pediatric hypertension, ambulatory blood pressure monitoring, white coat hypertension, masked hypertension, hypertensive target organ damage**

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## INTRODUCTION

The prevalence of hypertension (HTN) in children and adolescents ranges from 1 to 5% while prehypertension has been reported as high as 10% with rates of both HTN and prehypertension increasing over the past two decades (1, 2) Proper assessment of blood pressure (BP) in children and adolescents is important because pediatric BP is the strongest identified predictor for adult HTN (3, 4). Most recently, BP trajectory from childhood to young adulthood has been shown to be associated with target organ changes, specifically left ventricular mass index (LVMI) and carotid intima-media thickness (cIMT) (5). In the United States, approximately 32% of adults have HTN and worldwide, the prevalence of adult HTN is around 40% (6, 7). HTN contributes to 7.5 million deaths or 12.8% of all deaths globally per year (7). In addition to its morbidity and mortality, HTN costs $48 billion each year to the United States health-care system (8). Other common chronic diseases including coronary artery disease, renal disease, diabetes, and obesity are also adversely affected by and contribute to HTN, making it the primary risk factor-related cause of death worldwide (9). And thus, appropriate diagnosis and treatment of HTN in the pediatric population is important to prevent future cardiovascular disease and premature deaths as well as to decrease its economic burden.

Elevated BP in children and adolescents is often found during routine well child examinations or sports participation physicals. The National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents defines HTN in the Fourth Report as average systolic BP (SBP) and/or diastolic BP (DBP) ≥the 95th percentile for age, gender, and height on three or more occasions (10). Prehypertension is defined as average SBP and/or DBP between the 90th and 95th percentile. If the 90th percentile is higher than 120/80, which is the prehypertension threshold for adults, then 120/80 is also the threshold value used in adolescents (10). Clinic BP measurements have potential problems including improper technique, terminal digit preference, observer bias, and accommodation effect. In addition, BP measurements obtained in clinics may not necessarily reflect the true BP of an individual throughout the day while repeated ambulatory BP measurements using automatic devices may reflect more representative BP values and better risk stratification (11, 12). We now have pediatric ambulatory blood pressure monitoring (ABPM) practice guidelines and increasing clinical outcome data associated with ABPM parameters (13, 14). This review will briefly discuss the current use of pediatric ABPM and will have in-depth discussion on the state-of-the-art pediatric ABPM outcome data and promising clinical areas of expansion for ABPM to make a provocative argument for its use as standard of care in pediatric BP evaluation and management.

## ABPM USE IN PEDIATRICS

In order to overcome the limitations of clinic BP measurements mentioned above, ABPM has been in use in children and adolescents in the last 25–30 years (15, 16). A detailed description of ABPM and equipment has been published by the American Heart Association (AHA) in 2008 (13), and interested readers are encouraged to review this publication. In brief, a monitor is worn in the child's home environment, which should provide more accurate measurement of their true BP including during sleep. The device consists of a light-weight monitor and appropriately sized BP cuff worn on the non-dominant arm. Awake measurements occur every 15–20 min and sleep measurements occur every 20–30 min. Most authorities define a valid study as one with at least one valid reading per hour, and >40 BP readings in the 24 h period or >65% of all possible BP readings for a partial day study(13). Both oscillometric and auscultatory devices are available and validated for children (17). The largest cross-sectional pediatric ABPM study to formulate normative data used oscillometric devices (18, 19). Oscillometric devices usually have fewer erroneous readings and are easier to use than auscultatory devices (13). Mainly for these reasons, oscillometric ABPM devices are more commonly used in current pediatric clinical practice. During the study period, a diary is kept to record when the child is awake, asleep, and active in addition to any medication taken during the study period that may influence BP. ABPM may cause mild sleep disturbance in some children but is generally well tolerated (14).

When analyzing ABPM data, the mean SBP and DBP are calculated for the 24 h period as well as awake and sleep hours. BP load is calculated as the proportion of readings above threshold values expressed in percentages. In children and adolescents, threshold values are the 95th percentile of gender and height. ABPM is not performed in young children (<5 years old) because there are no normative data for this age group, and this age group is unlikely to tolerate the frequent BP measurements. Currently, indications for ABPM include confirming the diagnosis of HTN, evaluating for white coat hypertension (WCH) and masked hypertension (MH), assessing effectiveness of antihypertensive medication, and determining if symptoms can be attributed to drug-related hypotension (14). There are six categories of BP staging based on combination of clinic BP measurements and ABPM:

(1) BP is considered normal if clinic BP < 90th percentile, mean awake and sleep SBP and DBP < 95th percentile, and awake and sleep SBP and DBP loads are all <25%,
(2) WCH is when clinic BP ≥ 95th percentile and mean awake and sleep SBP and DBP < 95th percentile, and awake and sleep SBP and DBP loads are all <25%,
(3) Prehypertension is when clinic BP ≥ 90th percentile or >120/80 and mean awake and sleep SBP and DBP < 95th percentile, and awake or sleep SBP or DBP load is ≥25%,
(4) MH is when clinic BP < 95th percentile and mean awake or sleep SBP or DBP > 95th percentile, and awake or sleep SBP or DBP load is ≥25%,
(5) Ambulatory HTN is when clinic BP > 95th percentile and mean awake or sleep SBP or DBP > 95th percentile, and awake or sleep SBP or DBP load is 25–50%, and finally
(6) Severe ambulatory HTN is when clinic BP > 95th percentile and mean awake or sleep SBP or DBP > 95th percentile, and awake or sleep SBP or DBP load is >50%. These diagnosis categories are found in a table in the AHA 2014 Update (14).

## PEDIATRIC ABPM OUTCOME DATA

Adult ABPM studies have consistently reported superiority of ABPM parameters over clinic BP in predicting mortality, cardiovascular events, and target organ damage such as left ventricular hypertrophy (LVH) (20–22). In contrast to adults, there are no pediatric data available that correlate patient outcome with ABPM parameters largely due to very low incidence of mortality and cardiovascular events. However, there have been an increasing number of pediatric studies that have investigated ABPM parameters with target organ changes, including the heart, the arterial wall thickness, the kidneys, and central nervous system development. The following subsections will summarize published pediatric ABPM studies showing correlation between ABPM parameters with various target organ changes. This will be followed by subsections summarizing pediatric ABPM studies on WCH, MH, renal disease, and antihypertensive medication efficacy.

### Target Organ Damage

**Table 1** summarizes the pediatric ABPM studies that have investigated its parameters with target organ changes and their references. Among the target organs, the most studied is the heart, specifically the correlation between ABPM parameters and LVMI, which is a representation of left ventricular mass

**TABLE 1** | Summary of pediatric ambulatory blood pressure monitoring (ABPM) studies of association between its parameters and target organ damage.

| Organ | Target organ damage marker | Correlation with ABPM parameters? | Reference |
|---|---|---|---|
| Heart | Left ventricular mass index | Yes | (23, 24, 26–28) |
| Arterial vessels | Carotid intima-media thickness | Yes | (30–32) |
| Kidneys | Microalbuminuria | No | (34, 35) |
| Central nervous system | Executive function tests | Yes | (37–40) |

normalized by body surface area. It is now well established that left ventricular mass starts to increase with increasing BP even in the pediatric age range (23, 24), and LVH is an established risk factor of cardiovascular events in adults (25). There are several studies that have demonstrated that ABPM parameters are superior to clinic BP measurements in predicting higher left ventricular mass. Sorof et al. demonstrated LVMI strongly correlating with ABPM parameters such as mean SBP and SBP load where there was no correlation with clinic BP measurements (26). Maggio et al. found systolic ambulatory HTN by ABPM in 48% of obese children where clinic BP was normal in 55% of these hypertensive children, and after adjustment, LVMI was only associated with 24 h SBP (27). Richey et al. demonstrated that ABPM parameters such as higher 24 h SBP load predicted greater likelihood of increasing LVMI (28). Increased cIMT has been established as an independent risk factor for strokes in adults (29). There are now multiple pediatric studies showing an association between abnormal ABPM parameters with increased cIMT (30, 31). Further, obesity has also been associated with increased cIMT, but Lande et al. demonstrated several ABPM parameters to correlate strongly with cIMT in an age, gender, and body mass index matched study (32). In adults, microalbuminuria has been shown to be a marker of HTN-induced renal injury (33). However, pediatric ABPM studies have not demonstrated ABPM parameters to independently predict presence of microalbuminuria in non-diabetic children and adolescents to date (34, 35).

There is fairly extensive adult literature, which demonstrates that HTN is associated with poorer cognitive performance including learning and memory, executive functions; and visuospatial, visuoconstructional, psychomotor, and perceptual abilities, and chronic uncontrolled HTN predicts cognitive decline over time (36). More recently, there is emerging preliminary data, which suggest that children and adolescents with primary HTN are associated with neurocognitive deficits when compared to normotensive controls. Early studies in children on the link between HTN and cognitive function include a cross-sectional study that demonstrates children with elevated clinic SBP have an independent association with lower digit span test scores, which is a measure of short-term memory, attention, and concentration (37). This was followed by a matched longitudinal study of parental ratings of executive function of children with ABPM confirmed primary HTN. At the time of initial diagnosis, hypertensive children had lower parental rating of executive function compared to matched normotensive children (38). After 1 year of antihypertensive therapy, ABPM demonstrated improved BP in the hypertensive group, which also correlated with improvement in parental ratings of their executive function (39). Most recently, a multicentered study of neurocognition in children demonstrated that children with ABPM confirmed untreated primary HTN had lower performance on neurocognitive testing, in particular, on measures of memory, attention, and executive functions, compared to normotensive matched controls (40).

In summary, the above published studies suggest that proper diagnosis of HTN by ABPM in children and adolescents has the potential to prevent and/or to treat target organ damages, in particular, the heart, the arterial vessels, and the central nervous system, which may not be possible with clinic BP measurements alone.

## White Coat Hypertension

White coat hypertension in children and adolescents may be fairly common as studies have reported a wide range of prevalence of 13–52% of children with elevated clinic BP measurements (41–43). ABPM serves an important role in the initial evaluation of elevated BP measurement as misdiagnosis of HTN in patients with WCH may lead to unnecessary testing and treatment, which may cause adverse side effects and events and will add unnecessary health care cost. The clinical significance of WCH is not clear at this point in children and adolescents, but there are studies to suggest that it may represent a prehypertensive state. Pediatric ABPM studies suggest that WCH may result in intermediate target organ changes (41, 44). In a study where age, gender, and BMI were matched for ABPM confirmed WCH subjects with confirmed hypertensive subjects and normotensive subjects, the mean LVMI of WCH subjects was between that of normotensive and hypertensive subjects. The difference between the WCH subjects and normotensive subjects was statistically significant (45). Another study found that ABPM confirmed WCH subjects tended to have higher LVMI than normotensive subjects but lower than hypertensive subjects, although no statistically significant differences were found between the groups (41). There is currently no practice guideline on laboratory and imaging evaluation or subsequent follow-up of children and adolescents with WCH, but efforts are underway for longitudinal studies for children and adolescents with WCH.

## Masked HTN

The prevalence of MH in general pediatric population has been reported to be just under 10% (42, 46) and around 35–50% in children and adolescents who have risk factors for HTN such as chronic kidney disease (CKD) and post-coarctation of aorta repair (47–49). Currently, the mechanism of MH is still unclear. There are convincing data to suggest that left ventricular mass changes detected in children and adolescents with MH is very similar to those with sustained HTN (42, 46). Thus, identifying patients with MH is critical so target organ damages can be reversed and to potentially delay cardiovascular events. Diagnosis of MH is difficult since performing ABPM in all pediatric patients with normal clinic BP measurements is impractical. Identifying children with risk factors for MH with conditions discussed in sections below

and/or family history of early HTN and cardiovascular events is critical since ABPM could potentially "unmask" their HTN and reduce cardiovascular risk factors. Similar to WCH, further studies are needed so that evidence-based practice guidelines could be formulated in order to identify which pediatric populations should undergo ABPM to identify MH.

## CKD and Renal Transplantation

One of the most important populations to properly diagnose HTN is children with CKD as HTN is a well-known modifiable risk factor for progression of CKD (47, 50–52). These patients can often be missed as having HTN because of an increased risk for MH compared to the general population (49). A cross-sectional analysis of CKD in Children cohort with CKD stage 2 through 4, ages 9 through 15 years, found 38% of participants had MH and 18% had HTN confirmed by ABPM (49). Seventeen percent of this cohort had LVH with 34% from the MH group and 20% with confirmed HTN with increase in LVH prevalence from 19 to 39% over a 2-year period (49). Most importantly, the reduction in the rate of progression of CKD by tight BP control was demonstrated by the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial where intensified ABPM-guided HTN therapy over a 5-year period led to a 35% reduction in subjects with 50% decline in renal function or progression to end stage renal disease (52).

Hypertension implication in the renal transplant children and adolescents is similar to CKD population including its high prevalence, cardiovascular significance, and prognosis of allograft. When ABPM was used in renal transplant patients, prevalence of MH was found to be around 25–45%, and prevalence of uncontrolled HTN among treated patients ranged between 18 and 82% with median prevalence of 53% suggestive of the importance of routine use of ABPM in post-renal transplant population (53). Yearly ABPM-guided HTN treatment in 22 renal transplant patients after median follow-up of 9 years showed 14 of 17 children with treated HTN had excellent BP control, and the prevalence of LVH was only 4.5% with no progression of cIMT (54). Last, tighter BP control by annual ABPM-guided therapy resulted in normotensive group to have stabilization of the allograft function at 2 years after transplantation, and in contrast, the hypertensive group had a statistically significant decline in allograft function suggestive of preservation of allograft function with better BP control (53).

Thus, based on these published reports in CKD and post-renal transplant children and adolescents, the use of ABPM appears to be critical in their longitudinal follow-up not only to properly detect HTN but also to treat their HTN to slow down the progression of CKD or to preserve their allograft function.

## Antihypertensive Medication Efficacy

Ambulatory blood pressure monitoring is not only an effective way to properly diagnose HTN at the onset but it is also an effective way to determine the efficacy of HTN therapy. Seeman et al. demonstrated that nearly half of the pediatric patients on antihypertensive medications were found to have uncontrolled HTN by ABPM parameters. In addition, 35% of this study population had reclassification of controlled or uncontrolled HTN after having ABPM from their original classification based on clinic BP measurements, and the prevalence of LVH was significantly higher in uncontrolled HTN group compared to controlled HTN group (55). Similarly, Halbach et al. found that performing ABPM resulted in 63% of treated hypertensive children to have their medication changed (56). Last, Flynn also reported 4 out of 7 patients requiring adjustment of antihypertensive medications after undergoing ABPM (57). Thus, these studies are convincing of the clinical usefulness of ABPM for longitudinal BP assessment in efficacy of treated hypertensive children and adolescents.

Ambulatory blood pressure monitoring's superiority at detecting treatment-induced BP changes compared to clinic BP measurements makes it ideal for its use in pediatric antihypertensive medication clinical trials. Using the ESCAPE trial cohort, Gimpel et al. showed that SD of ABPM responses were up to 39% smaller than those of clinic BP measured responses. Using power analysis, they showed that depending on the magnitude of the aimed BP reduction, sample size could be reduced by 57–75% with the use of ABPM, which would be critical in reducing the number of hypertensive subjects receiving placebo drugs (58).

# CLINICAL AREAS OF EXPANSION FOR ABPM

The use of ABPM in children and adolescents has become more prevalent especially when evaluating to distinguish sustained HTN from WCH for elevated clinic BP measurements and in patients with kidney diseases including CKD and post-renal transplantation as discussed in the previous section. However, there is a wide spectrum of clinical areas where ABPM is not routinely used currently and where it could be very useful in detecting hypertensive patients. **Table 2** demonstrates these conditions in which ABPM can potentially be utilized even if they have normal clinic BP measurements.

## Coarctation of Aorta

Coarctation of aorta is one of the more common causes of secondary HTN in pediatrics and makes up about 2% of all children and adolescents with HTN (59). More recent reports have also demonstrated long-term mortality and morbidity even after

**TABLE 2** | Clinical areas of expansion for ambulatory blood pressure monitoring (ABPM).

| Potential clinical areas where ABPM should be used to detect masked HTN |
|---|
| Coarctation of aorta |
| Non-renal solid organ transplantation |
| Hematopoietic transplantation |
| Diabetes mellitus |
| Obstructive sleep apnea |
| Turner syndrome |
| William syndrome |
| Neurofibromatosis, type I |
| Sickle cell disease |

successful coarctation repair. The survival rates of coarctation repair patients have been reported to be up to 20% less compared to age- and gender-matched populations mainly due to cardiovascular disease (60), and rates of persistent aortic hypoplasia and HTN have been reported to be as high as 20–48 and 21–42%, respectively (61, 62). Further, even in post-coarctation repair patients where the aortic arch were reported to be normal, 27% had hypertensive clinic BP measurements, 61% had HTN diagnosed by ABPM, and 55% had LVH with higher rates of LVH in ABPM confirmed hypertensive group compared to normotensive group (63). Therefore, ABPM appears to be a critical tool in following BP in post-coarctation of aorta repair patients (60, 63).

## Non-Renal Solid Organ Transplantation

The literature on the use of ABPM is scarce in non-renal solid organ transplantation. Because of the frequent uses of glucocorticoids and nephrotoxic agents such as calcineurin inhibitors and higher prevalence of CKD, HTN has been reported to be significantly higher than the general pediatric population in liver, intestinal, and heart transplantation (64–67). In the adult cardiac transplantation data registry, HTN incidence is 90% at 5 years after transplantation, and it is one of the main risk factors for cardiac allograft vasculopathy, the fourth leading cause of death at 10 years after transplantation (68). In adult liver transplant patients, cardiovascular disease is the second most common cause of non-liver death behind cancer (69). There have been a small number of pediatric ABPM studies in liver and heart transplant recipients, and they have concluded that clinic BP readings poorly correlate with ABPM parameters (70, 71). Therefore, ABPM should be strongly considered as part of routine posttransplant surveillance evaluation for precise diagnosis of HTN so that onset of cardiovascular mortality and morbidity may be delayed. This is also a fertile area for future and larger studies to investigate the exact prevalence of HTN in these high risk groups.

## Hematopoietic Cell Transplantation

Similarly, survivors of hematopoietic cell transplantation patients have been reported to have higher risk of HTN from multifactorial etiologies including the use of glucocorticoids, nephrotoxic medications including calcineurin inhibitors and various chemotherapy agents, total body irradiation, graft versus host disease, and kidney injury (72, 73). In a late mortality analysis of hematopoietic cell transplantation patients with median age of 25.9 years old, these survivors have a 2.3-fold increase in risk for premature cardiovascular related death (74). Seventy percent of children and adults have HTN during the first 2 years after hematopoietic cell transplant (72). Again, ABPM could be very useful aspect of routine posttransplant surveillance evaluation for the same reasons as the solid organ transplant recipients.

## Type I Diabetes Mellitus

Ambulatory blood pressure monitoring also appears to be promising tool in following pediatric patients with type I diabetes mellitus (T1DM). Children with T1DM were frequently found to have ABPM confirmed HTN with most of them being nocturnal HTN suggestive of the important role of ABPM in this population (75). Perhaps more clinically relevant, there was an independent association between nocturnal HTN detected on ABPM with development of microalbuminuria, which is a marker of diabetic nephropathy, in a cohort of adolescents and young adults with T1DM followed for more than 5 years (76). Combining the findings of these studies, ABPM could be used routinely in children and adolescents with T1DM not only to diagnose HTN earlier but also to use it longitudinally for more strict nocturnal BP control to prevent or to slow the progression of diabetic nephropathy.

## Obstructive Sleep Apnea

One of the more common comorbidity of obesity and obesity-related HTN is obstructive sleep apnea, and the use of ABPM appears to be helpful in this population. In a tertiary care hospital-based population, there was an independent association between apnea–hypopnea index and nighttime SBP and mean arterial pressure adjusting for adiposity variables suggestive of children with moderate-to-severe obstructive sleep apnea having higher ABPM parameters compared with children who were primary snorers (77). Similarly, in children with apnea–hypopnea index >5/h, ABPM parameters such as 24 h mean BP and BP loads were significantly increased, and perhaps more clinically relevant, early morning BP surge was more likely to occur in these children (78). Thus, ABPM could be very useful in detecting these abnormal BP patterns even if they have normal clinic BP in otherwise high-risk group of children and adolescents for future cardiovascular disease. Although not completely curative, adenotonsillectomy improved some of the ABPM parameters (79), suggestive of improvement in obstructive sleep apnea having contribution to lowering of BP. Best to our knowledge, although no pediatric study to date has shown lowering of BP with continuous positive airway pressure, adult literature has shown significant decreases in daytime and nighttime SBP and DBP with improvement in number of patients with prehypertension from 94 to 55% and MH from 30 to 5% (80).

## Other Pediatric Conditions with HTN Association

There are relatively common conditions in children and adolescents known to increase the risk of HTN including polycystic ovary syndrome, William syndrome, Neurofibromatosis type I, and Turner Syndrome. Single centered studies in each of these conditions have identified higher detection rates of HTN by ABPM compared to clinic BP measurements (81–85). Women with polycystic ovary syndrome have been found to have increased cardiovascular disease risk factors earlier in life (86), while women with Turner syndrome have a markedly increased incidence of ischemic heart disease, HTN, and stroke (87). Both children and adults with Williams syndrome have been found to have increased cardiovascular disease risk factors (82, 88). Traditionally, patients with sickle cell disease were observed to have lower clinic BP measurements largely attributed to poor urinary concentrating ability. However and surprisingly, a cross-sectional analysis of children with sickle cell disease

found 10% to have elevated clinic BP measurements and 44% to have ABPM diagnosed HTN suggestive of high rates of MH in this population. Further, 59% of subjects were found to have impaired SBP nocturnal dipping and 13% had reversed nocturnal dipping (89).

In summary, there are a relatively large number of clinical areas discussed in this section where ABPM is currently underutilized but should be used routinely to detect MH and to follow BP longitudinally in order to prevent and to delay the onset of cardiovascular disease in growing number of high risk children and adolescents with chronic conditions. The 2016 European Society of HTN guidelines for the management of high BP in children and adolescents recommends ABPM for pediatric patients with diabetes mellitus type 1 and 2, CKD, solid organ transplants including renal, liver and heart, and severe obesity with or without sleep disordered breathing (90).

## COST EFFECTIVENESS OF ABPM

Traditional practice in pediatrics for a new diagnosis of HTN often included extensive evaluation of secondary causes of HTN including laboratory investigation, imaging studies, and target organ damage assessment, most often echocardiogram. A cost analysis at a pediatric HTN clinic where the protocol was to perform ABPM on all patients with stage I HTN clinic BP measurements found projected saving of $2.4 million for every 1,000 patients given their WCH rate of 46% (91). The cost savings were mainly attributed to not doing renal ultrasonography and echocardiogram on children with WCH, and authors speculated that the ABPM cost savings could be even higher as laboratory testing and number of clinic visits would be reduced for children with WCH. Davis et al. found that universal ABPM use at a pediatric HTN referral center accrued the lowest average charge per

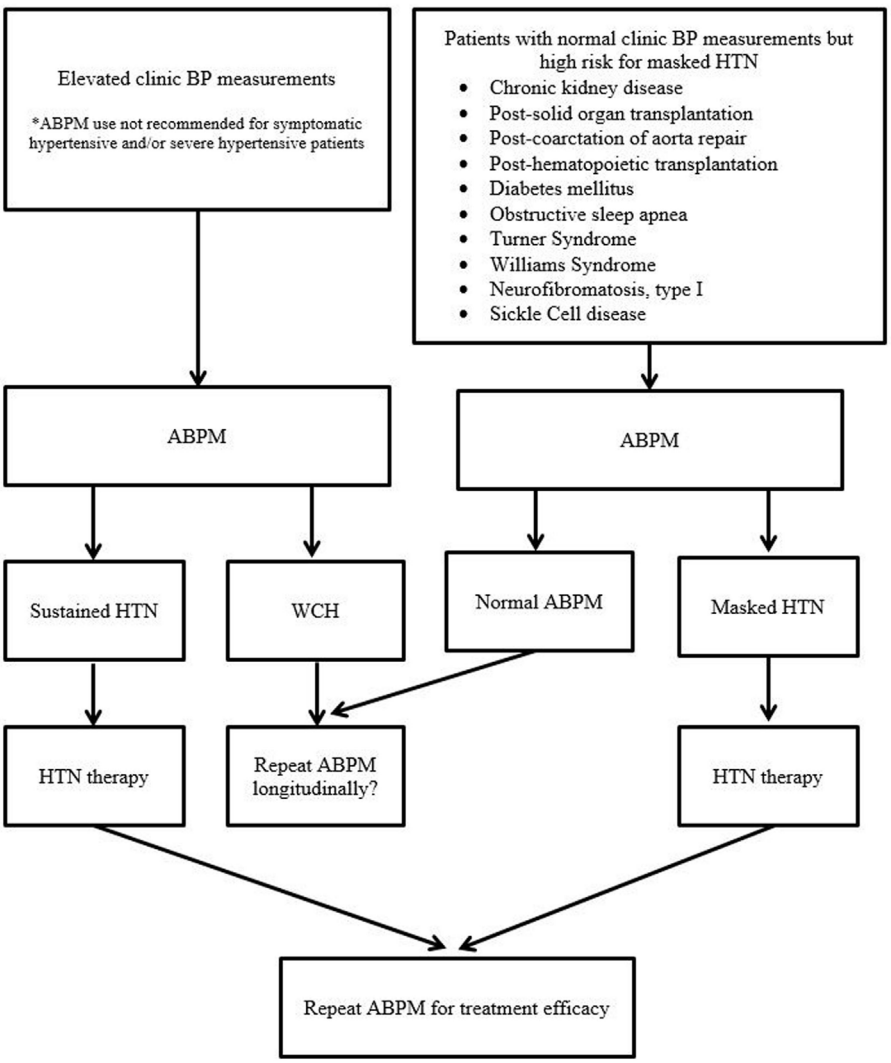


**FIGURE 1** | Schematic diagram of various points of ABPM utility in pediatric hypertension evaluation and management (BP, blood pressure; HTN, hypertension; ABPM, ambulatory blood pressure monitoring; WCH, white coat hypertension).

hypertensive youth identified and concluded that its universal use may be the most economically and clinically efficient diagnostic strategy (92).

## LIMITATIONS OF ABPM

There are some limitations in our current knowledge and clinical use of pediatric ABPM. The most glaring is the need for more comprehensive normative ABPM data (14, 90). The ABPM normalized data being used today are based on values from the German Working Group on Pediatric HTN, which evaluated 1,141 children aged 5–20 years (18, 19). These children were a homogeneous Caucasian central European population, which is likely not generalizable in children of different races worldwide, and thus, normative data based on larger and multiethnic cohort are greatly needed. Another area in need of improvement is the development of BP measurement device that can measure DBP more accurately as this German normative data have almost flat DBP curve across all height in both genders (93).

Ambulatory blood pressure monitoring monitor availability in pediatric clinics is currently suboptimal. Based on a recent on-line survey among pediatric nephrologists at centers belonging to the Midwest Pediatric Nephrology Consortium in North America, 94% of the survey responders were at centers where ABPM was available, but 57% of responders stated that patients sometimes had to wait to have ABPM as monitors were not available at the time of the visits. This inconvenience is likely attributable to approximately 75% of survey responders practicing at centers owning <10 monitors (publication in press). Last, another potential barrier is the cost to start an ABPM program and its income potential. One ABPM monitor along with the software costs around $3,500–$4,000. In the United States, many government-based and other private health insurances either do not cover or have fairly low reimbursement rate for ABPM for children despite the cost effectiveness mentioned above and ABPM published guidelines starting in 2008. It is estimated that 190–200 ABPM studies would need to be performed to recover the initial starting cost (94). With wide spectrum of potential clinical areas of expansion as discussed above, better monitor availability at pediatric HTN clinics will be vital in ABPM becoming routine part of BP evaluation and management.

## CONCLUSION

The health and economic burden of HTN is unquestioned worldwide. Based on recent data to suggest BP tracking from childhood to adulthood with target organ damages, earlier and proper diagnosis of HTN by ABPM is vital in the first step to prevent and to delay cardiovascular consequences of HTN. By properly identifying children and adolescents with WCH, ABPM can also reduce the number of children and adolescents undergoing unnecessary medical tests and experiencing adverse effects from unnecessary therapy. Routine use of ABPM appears to also save costs to the health-care system. Pediatric ABPM studies in the last 25–30 years are starting to demonstrate its superiority in target organ outcomes over clinic BP measurements. In addition, there are multiple clinical areas where ABPM use is currently infrequent, but its use may be very valuable in longitudinal care of many children and adolescents with chronic conditions. **Figure 1** is a schematic diagram of various points where ABPM can be utilized in pediatric HTN. Certainly, we currently have both scientific and practical shortcomings in the pediatric use of ABPM, but this also provides wealth of future research target areas. Thus, in moving forward, we advocate ABPM to be standard of care in the field of pediatric HTN in both clinical and research settings.

## AUTHOR CONTRIBUTIONS

CP and YM performed comprehensive literature search, drafting and editing of manuscript, final approval of the version, and agreed to be accountable for all aspects of the work.

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REVIEW
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# Genetic Programming of Hypertension

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The heritability of hypertension (HTN) is widely recognized and as a result, extensive studies ranging from genetic linkage analyses to genome-wide association studies are actively ongoing to elucidate the etiology of both monogenic and polygenic forms of HTN. Due to the complex nature of essential HTN, however, single genes affecting blood pressure (BP) variability remain difficult to isolate and identify and have rendered the development of single-gene targeted therapies challenging. The roles of other causative factors in modulating BP, such as gene–environment interactions and epigenetic factors, are increasingly being brought to the forefront. In this review, we discuss the various monogenic HTN syndromes and corresponding pathophysiologic mechanisms, the different methodologies employed in genetic studies of essential HTN, the mechanisms for epigenetic modulation of essential HTN, pharmacogenomics and HTN, and finally, recent advances in genetic studies of essential HTN in the pediatric population.

**Keywords: genetics, hypertension, children, epigenetics, pharmacogenomics, pediatrics**

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## INTRODUCTION

Hypertension (HTN) is a serious public health issue affecting both children and adults. Between 2009 and 2012, approximately 32.6% of adults in the US were reported to have HTN (1). In children and adolescents between 3 and 18 years of age, the prevalence of HTN has been reported to be 3.6% (2). Morbidity and mortality from HTN continue to be high in adults, with HTN accounting for an estimated 45% of deaths due to cardiac disease and 51% of deaths from strokes (3). Despite its widespread prevalence, however, the etiology of essential HTN remains largely unknown. A growing body of evidence supports the observation that HTN results from a complex interplay of genetic, epigenetic, and environmental factors. Genetic factors are thought to contribute to approximately 30–60% of blood pressure (BP) variation (3, 4). However, known genetic factors explain only 3% of BP variance (5), underscoring the fact that many genetic variants have yet to be discovered. Moreover, these findings suggest that other factors, such as gene–gene interactions and epigenetics, may play a vital role in the etiology of HTN.

The clinical implications for deciphering the genetic factors that contribute to variations in BP and response to antihypertensive medications are significant. Knowledge of an individual's predisposition to HTN can help with early implementation of preventive measures and formulation of effective therapeutic plans. In addition, pharmacogenomic information can help with the selection of personalized medication regimens, which may optimize therapeutic responses and help to reduce health-care costs. In this review, we discuss the various forms of monogenic HTN, the different study designs used to investigate the genetic epidemiology of essential HTN, the epigenetics of essential HTN, HTN pharmacogenomics, and recent advances in the genetics of essential HTN in children.

## MONOGENIC HTN

Monogenic HTN syndromes refer to hypertensive disorders that follow Mendelian inheritance patterns due to single-gene mutations. Most monogenic forms of HTN are associated with volume expansion and low serum renin levels. A summary of the various types of monogenic HTN is provided in **Table 1**. **Figure 1** presents the different pathophysiologic mechanisms that are involved in monogenic forms of HTN.

### Glucocorticoid-Remediable Aldosteronism (GRA)/Familial Hyperaldosteronism (FH) Type I

Glucocorticoid-remediable aldosteronism, an autosomal dominant disorder, was the first monogenic HTN syndrome to be identified (6). GRA is caused by a chimeric gene formed from the fusion of the promoter region of the 11 β-hydroxylase gene (*CYP11B1*) with the coding regions of the aldosterone synthase gene (*CYP11B2*) on chromosome 8q (7, 8). As a result of this chimeric gene, aldosterone production is activated by ACTH and becomes independent of renin regulation (7). The development of hyperaldosteronism, with resultant salt and water retention, leads to HTN. Patients with GRA typically present with mild hypokalemia, metabolic alkalosis, and low plasma renin levels. The early onset of GRA before 21 years of age and the development of significant hypokalemia with a thiazide diuretic are important clinical features of this condition (9).

Some patients with GRA may exhibit unique features such as cerebral aneurysms and intracranial bleeding. Therefore, screening by brain MRI at the onset of puberty in patients with GRA has been recommended (10). As the name suggests, GRA is remediable by glucocorticoids since they inhibit ACTH production, the stimulus for aldosterone production in GRA (11).

#### Other Rare Forms of FH

(i) FH type II: FH type II is characterized by the familial occurrence of aldosterone-producing adenomas or bilateral idiopathic adrenal hyperplasia that is unresponsive to glucocorticoids. This condition has a very similar clinical presentation to sporadic primary hyperaldosteronism (12); the only distinguishing feature is that a greater number of family members from the same kindred are affected by FH type II (13). The gene responsible for FH type II remains unknown and, therefore, diagnosis is usually challenging and based on exclusion of other conditions. Treatment of FH type II consists of administration of mineralocorticoid receptor antagonists and/or unilateral adrenalectomy for aldosterone-producing adenomas (14).

(ii) FH type III: The gene *KCNJ5* encodes an inward rectifier potassium channel Kir3.4. In FH type III, a gain-of-function mutation in the *KCNJ5* gene causes loss of membrane

**TABLE 1** | Summary of the various forms of monogenic HTN.

| | GRA | AME | CAH | Liddle | Gordon |
|---|---|---|---|---|---|
| Mode of inheritance | AD | AR | AR | AD | AD |
| Electrolyte abnormality | Hypokalemia/normal potassium<br>Metabolic alkalosis | Hypokalemia/normal potassium<br>Metabolic alkalosis | Hypokalemia/normal potassium | Hypokalemia/normal potassium | Hyperkalemia/normal potassium<br>Mild metabolic acidosis |
| Time of onset of HTN | Early | Early onset for severe phenotype | Early | Early | Late |
| HTN severity | Moderate–severe | Moderate–severe | Severe | Moderate–severe | Severe |
| Aldosterone/renin level | Elevated aldosterone levels. Low renin and angiotensin II levels | Very low aldosterone and low renin levels | Low renin and aldosterone levels | Low renin and aldosterone levels | Aldosterone levels can vary. Low renin levels |
| Mechanism for HTN | Increased renal absorption of salt and water | Stimulation of MC receptor by cortisol | Excess cortisol precursors activate MC receptors | Increased renal absorption of salt and water | Increased Na–Cl cotransporter activity in the distal convoluted tubule |
| Genetic cause | *CYP11B1* gene fused with *CYP11B2* gene on chromosome 8q | Inactivating mutation in *HSD11B2* gene | Type IV: *CYP11B1* gene<br>Type V CAH: *CYP17A1* gene | Mutation in *SCNN1B/SCNN1G* gene on chromosome 16p | *WNK 1* and *4* mutation (2 different loci on chromosome 12 and 17) |
| Other features | Cerebral hemorrhage<br>Celtic ancestry | Similar presentation as licorice abuse | Type IV: ambiguous genitalia in girls, precocious puberty in boys<br>Type V: primary amenorrhea in girls, ambiguous genitalia in boys | | Hypercalciuria |
| Treatment | Glucocorticoids, amiloride, triamterene | Spironolactone, eplerenone, amiloride | Steroids, spironolactone, eplerenone | Low-salt diet. Triamterene or amiloride | Low-dose thiazides |

*GRA, glucocorticoid-remediable aldosteronism; AME, apparent mineralocorticoid excess; CAH, congenital adrenal hyperplasia; AD, autosomal dominant; AR, autosomal recessive; MC, mineralocorticoid; HTN, hypertension.*

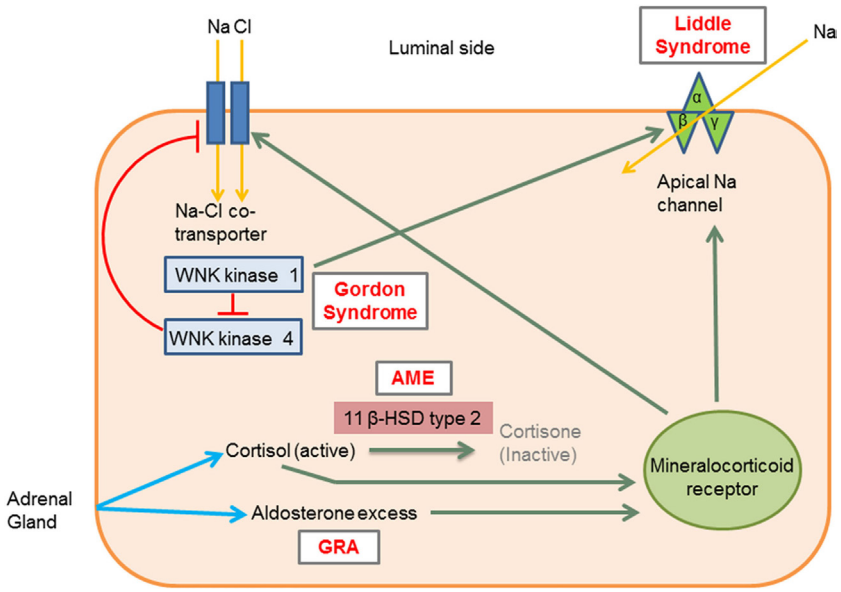


**FIGURE 1** | Molecular mechanisms involved in the different types of monogenic hypertension (HTN). Liddle syndrome: gain-of-function mutation in the gene encoding the apical epithelial sodium channel (ENaC) causes increased sodium absorption and subsequent HTN. Gordon syndrome: WNK1 normally inhibits WNK4, which in turn inhibits the Na–Cl cotransporter (NCC). WNK1 gain-of-function and WNK4 loss-of-function mutation increases the activity of the NCC leading to increased salt and water retention. AME: 11 β-hydroxysteroid dehydrogenase type II enzyme deficiency results in reduced cortisol conversion to cortisone (inactive form). Cortisol binds to the mineralocorticoid receptor and leads to signs of mineralocorticoid excess. GRA: a chimeric gene leads to excess aldosterone production, which acts on mineralocorticoid receptors. 11β HSD type II, 11 β-hydroxysteroid dehydrogenase type II enzyme; AME, apparent mineralocorticoid excess; GRA, glucocorticoid-remediable aldosteronism; Activation, green arrows; Inhibition, red lines with barheads. [Adapted from Simonetti et al. (18)].

ion selectivity, triggering membrane depolarization and increased calcium entry into the adrenal glomerulosa cells. This in turn leads to hyperaldosteronism, HTN, adrenal hyperplasia, and severe hypokalemia (13, 15). Treatment usually requires bilateral adrenalectomy, especially in drug resistant cases.

(iii) FH type IV: discovered in five unrelated families by whole-exome sequencing, FH type IV is due to a gain-of-function mutation in the *CACNA1H* gene that encodes a T-type calcium channel (13). This mutated channel allows excess calcium entry into the adrenal glomerulosa cells and subsequent hyperaldosteronism (16). Mineralocorticoid receptor antagonists may be used for the treatment of FH type IV (14).

## Syndrome of Apparent Mineralocorticoid Excess (AME)

The syndrome of AME is an autosomal recessive disorder caused by an inactivating mutation in the *HSD11B2* gene, which encodes the 11β-hydroxysteroid dehydrogenase type II enzyme. This enzyme normally converts cortisol to the less active metabolite cortisone. With the inactivating mutation, excess cortisol accumulates and binds to the mineralocorticoid receptor, leading to symptoms of mineralocorticoid excess (17). Both mild and severe phenotypes of AME have been described. The mild AME phenotype manifests as mild HTN later in life with rare or no electrolyte abnormalities, while the severe phenotype presents early in life with severe HTN, failure to thrive, and early end organ damage (18). These phenotypic differences are likely related to differences in the level of enzyme expression. Whereas 11 β-hydroxysteroid dehydrogenase type II enzyme expression is almost absent in the severe phenotype of AME, it is present in varying degrees in the mild form of AME as a result of different mutations in the *HSD11B2* gene (19, 20).

Other clinical features of AME include hypokalemia with an increased trans-tubular potassium gradient, metabolic alkalosis, hypercalciuria, and nephrocalcinosis (18, 19). These clinical features are similar to those seen in licorice abuse, because licorice inhibits the same enzyme involved in AME. Genetic testing may be done to confirm the diagnosis. Treatment usually consists of mineralocorticoid receptor antagonists (spironolactone and eplerenone), epithelial Na channel blockers (amiloride), and thiazides (for hypercalciuria) with potassium supplementation as needed (18).

Geller syndrome, otherwise known as HTN exacerbated by pregnancy, is another mineralocorticoid excess syndrome caused by an activating mineralocorticoid receptor gene mutation. As a result of this mutation, the mineralocorticoid receptor loses its specificity for aldosterone and is activated by both aldosterone and progesterone. Inherited in an autosomal dominant manner, Geller syndrome leads to early HTN, which is exacerbated during pregnancy due to activation of the mineralocorticoid receptors by progesterone. Clinical features include normal serum potassium levels in the setting of low serum renin and aldosterone levels (21).

## Congenital Adrenal Hyperplasia (CAH)

Congenital adrenal hyperplasia results from defects in enzymes involved in cortisol synthesis (14). In type IV CAH (due to 11 β-hydroxylase deficiency) and type V CAH (due to 17 α-hydroxylase deficiency), the loss of cortisol feedback inhibition on the pituitary results in increased ACTH production and adrenal hyperplasia. This in turn leads to the accumulation of cortisol precursors, which cause increased salt and water uptake and subsequent HTN *via* activation of mineralocorticoid receptors. As a result, aldosterone production is suppressed (18).

Characteristic features of type IV CAH are precocious puberty, virilization due to excess sex hormone production with androgenic action, and early onset HTN (22). Type IV CAH is treated with steroids and mineralocorticoid receptor antagonists such as spironolactone for HTN.

Type V CAH has features opposite to type IV CAH due to sex hormone synthesis blockade, which manifests as delayed sexual development in girls and ambiguous genitalia in boys. Type V CAH is treated with steroids and sex hormones, in addition to mineralocorticoid receptor antagonists for HTN (18).

## Liddle Syndrome

Liddle syndrome is an autosomal dominant condition caused by a gain-of-function mutation in the *SCNN1B/SCNN1G* gene (located on chromosome 16p), which encodes the β and γ subunits of the epithelial sodium channel ENaC. This mutation causes an inability of ENaC to be removed from cell surfaces of the cortical collecting tubules, leading to increased sodium reabsorption and subsequent HTN (23). Patients with Liddle syndrome typically present with hypokalemia, metabolic alkalosis, low renin and aldosterone levels, and early onset HTN. Treatment includes a low salt diet and ENaC inhibitors, such as amiloride and triamterene (18).

## Pseudohypoaldosteronism Type II (Gordon Syndrome, Familial Hyperkalemic HTN)

Gordon syndrome is characterized by autosomal dominant inheritance of serine–threonine kinase gene (*WNK1* and *4*) mutations. Normally, WNK1 inhibits the function of WNK4, while WNK4 inhibits the expression of the Na–Cl cotransporter (NCC) (24). Therefore, a gain-of-function mutation in *WNK1* and loss-of-function mutation in *WNK4* collectively result in increased NCC expression and activity in the distal convoluted tubule (14). This leads to salt and water retention, followed by HTN (25). The increased salt reabsorption reduces sodium delivery to the cortical collecting duct, facilitating increased potassium absorption and hyperkalemia, which is typical of Gordon syndrome. ROMK channels, which aid in potassium excretion, can also be inhibited by the *WNK4* mutation, further causing hyperkalemia (8). Other metabolic abnormalities in Gordon syndrome include mild hyperchloremic metabolic acidosis, hypercalciuria, low urinary sodium excretion (26), low serum renin, and varying aldosterone levels. Metabolic abnormalities tend to occur earlier than HTN, which tends to present in adolescence or adulthood (27). Treatment of Gordon syndrome consists of low dose thiazide diuretics.

## HTN with Brachydactyly

Hypertension with brachydactyly is caused by a mutation in the *PDE3A* gene which encodes phosphodiesterase 3A (14). Patients affected by this syndrome have severe salt-independent HTN with short phalanges and metacarpals (28). The mechanism for HTN in this syndrome remains unknown, although it has been suggested that vascular smooth muscle cell hyperplasia and increased vascular resistance may play a role (28).

# GENETIC EPIDEMIOLOGY STUDY DESIGNS FOR ESSENTIAL HTN

Traditional pedigree-based analyses are not very effective in genetic studies of essential HTN due to its complex nature. Therefore, other methodologies have been used to study the genetic epidemiology of essential HTN. The following section contains a brief description of the different study designs that have been employed in investigating the genetics of HTN, with a special focus on genome-wide association studies (GWAS) (7).

## Non-Parametric Linkage Analysis

Linkage refers to the tendency of two genes to be inherited together when they are in close physical proximity to each other on a chromosome (29). Based on this phenomenon, linkage analysis aims to locate the approximate position of a disease gene by using the location of a known marker gene (29, 30). The marker gene refers to a DNA sequence that has a known physical location and has a detectable phenotype. By investigating whether markers and disease traits co-segregate, linkage analysis can approximate the location of the disease gene (29). Non-parametric linkage analysis (or model-free analysis) is used when details regarding the disease, such as the genetic mode of inheritance, are not known (30). This method is particularly useful in studying complex diseases, such as essential HTN, where the mode of inheritance is unknown. Non-parametric linkage analysis of affected sibling pairs can provide significant insights into a particular HTN phenotype (7). However, a limitation of this method is that many affected sibling pairs are often required to achieve adequate power to detect statistically significant differences.

### Discordant Sibling Pair Analysis

Discordant sibling pair analysis is a type of genetic linkage analysis that traces quantitative genetic trait loci. In this method, the square of the BP difference is measured as a function of the number of alleles that a sibling pair shares at known marker loci (31). If siblings with very discordant BPs are identified, then their genetic variation can be studied. The disadvantage of this method is that the process of identifying siblings with significant BP discordance can be quite challenging (7).

## Association Studies

Association studies are based on comparisons of a particular allele frequency between cases and unaffected controls/cohorts. These studies aim to determine whether an association is present between the particular allele and a disease trait (32). Association studies can be family-based or population-based (comprising

unrelated individuals) and may use a case–control or cohort approach. Population-based studies are more widely used than family-based studies, since fewer resources are required to enroll cohorts than family-based studies. Population-based studies may also require less genotyping (33). One advantage of family-based association studies, however, includes protection against population substructure-related bias. This is a selection bias that occurs when study subjects come from population subgroups with different ancestries (34). This results in spurious differences in allele frequency between cases and controls/cohorts (35). In family-based association studies, study subjects within each family come from the same source population, minimizing selection bias. Another advantage of family-based association studies is the higher likelihood of true linkage and association when significant findings are identified (33).

## Genome-Wide Association Studies

Based on the concept of linkage disequilibrium at the population level, GWAS attempt to identify the association between genetic variants or single-nucleotide polymorphisms (SNPs), and common disease traits in populations (36). SNPs are located in particular genetic loci and refer to variations in single nucleotides (14, 37).

The Wellcome Trust Case Control Consortium (WTCCC) study, conducted in 2007, was the first study that attempted to identify variants associated with HTN using GWAS; however, no significant association was identified (38). Small sample size and the use of HTN as a discrete variable are some of the reasons for the failure of the WTCCC to identify an association between SNPs and BP (14, 39). The use of HTN as a discrete variable (presence or absence of HTN), as opposed to a continuous variable (systolic BP or diastolic BP), decreases study power and has therefore become an important consideration in subsequent GWAS designs (40).

In 2011, the International Consortium for BP GWAS identified 29 SNPs that were associated with HTN (41, 42). Since then, more than 60 SNPs have been identified that affect BP *via* mechanisms of sodium handling, kidney function, vasoconstriction, and molecular signaling (43–45). Examples of some novel SNPs linked to systolic BP and diastolic BP in both children and adults that have been identified through GWAS are listed in **Table 2**.

Despite the identification of multiple SNPs associated with HTN, each of the common variants that have been discovered to this point appear to have only a small overall effect on BP (about 1 mmHg for systolic BP or 0.5 mmHg for diastolic BP) (41), with some rare variants noted to have a larger effect on BP (>1.5 mmHg) (55). These findings suggest that several genes may act in concert to modulate BP, and that other factors, such as gene–gene and gene–environment interactions, may contribute to BP variability.

A challenge of GWAS includes the difficulty in identifying the gene affected by the SNP, since the area of influence of the SNP may lie in distant genes (56). Some SNPs with genome-wide significance also exhibit pleiotropy and demonstrate strong independent links to more than one disease. For example, rs13333226 is independently associated with HTN and chronic kidney disease (57, 58).

Selection of cases and controls may also introduce a confounding bias in GWAS. False associations can be identified if the cases and controls are selected from different populations that have different baseline allele frequencies. This phenomenon is referred to as population stratification and may result when study subjects have different ancestries (35). Methods to address this issue include using genomic information to control for population structure, or using family-based study designs (29, 59). The selection of unaffected family members as controls in family-based study designs has the additional advantage of reducing environmental exposure confounders (60).

The recruitment of a large number of controls can be costly in GWAS due to the extent of genotyping involved. Thus, more studies are using genotypic information from subjects already enrolled as controls in other studies (60).

**TABLE 2** | Novel SNPs linked to elevated BPs identified through GWAS.

| Locus | Lead SNP | Encoded protein function | Reference |
|---|---|---|---|
| *HIVEP3* | rs7515635 | Modulates transcription | (46, 47) |
| *CSNK1G3* | rs6891344 | Serine/threonine protein kinase involved in phosphorylation | (46, 48) |
| *PSMD5* | rs10760117 | Subunit of ATP-dependent protease | (46, 49) |
| *MAP4* | rs319690 | Involved in assembly of microtubules | (14, 50) |
| *MOV10* | rs2932538 | Part of RNA helicase | (14, 51) |
| *ULK4* | rs3774372 | Serine/threonine kinase | (14, 52) |
| *CSK* | rs1378942 | Tyrosine kinase involved in actin remodeling | (53, 54) |

*SNP, single-nucleotide polymorphism; GWAS, genome-wide association studies.*

# EPIGENETICS OF HTN

Epigenetic phenomena refer to changes in gene expression in the absence of alterations of the DNA sequence itself, and include posttranslational histone modification, DNA methylation, and non-coding microRNAs (miRNAs) (61). Although epigenetic modifications are heritable and can be passed on through several generations, they can also be influenced by nutritional, pharmaceutical, fetal, and environmental factors, and may be reversible. Epigenetic events play critical roles in physiological processes such as cellular differentiation, by ensuring that only certain genes are expressed in specific cell types (3). Abnormalities in epigenetic events can lead to the development of HTN, and in fact, HTN has been linked to several epigenetic phenomena as discussed below (62).

## DNA Methylation

DNA methylation involves the covalent binding of a methyl group to cytosine, forming 5-methylcytosine (5mC) within CpG dinucleotide sequences (61). The methyl groups come from S-adenosylmethionine, the availability of which is dependent on folate metabolism. This association with folate metabolism provides the basis for the strong link between DNA methylation and nutrition (61). DNA methylation of CpG dinucleotides (often located in the promoter regions) results in inhibition of transcription and therefore gene silencing (63). The onset and severity of HTN have been reported to be associated with the extent of DNA methylation (64). Smolarek et al. quantified the amount of 5mC

in DNA from patients with essential HTN and found that lower levels of 5mC corresponded to higher stages of HTN (65). Lin et al. reported that hypomethylation of the angiotensin II type I receptor gene correlated with higher systolic and diastolic BPs. Smokers with HTN were also observed to have a lower level of methylation (66).

Interestingly, Meems et al. discovered that vitamin D-deficient parental rats had offspring with increased systolic and diastolic BPs (67). The offspring were found to have hypermethylation of the promoter region of the Panx1 gene. Furthermore, the offspring rats showed impaired endothelial relaxation, consistent with the fact that Panx1 encodes a hemichannel that plays a role in endothelial relaxation (67). These findings suggest that *in utero* nutritional status may affect childhood BPs; however, further research will be needed to determine whether prenatal and postnatal nutritional status have effects on the development of HTN in children (68).

### Histone Modification

Posttranslational modification of the N-terminal tail of histone proteins through processes such as methylation and acetylation can lead to changes in chromatin dynamics. This in turn leads to either decreased or increased gene expression (63). Both animal and human studies have shown associations between histone modifications and HTN. One such study reported that histone modifications resulted in angiotensin-converting enzyme 1 (ACE1) upregulation in organs from hypertensive rats (69). In human endothelial cells, cell-specific histone modifications were found to regulate mRNA levels of endothelial nitric-oxide synthase (70). Endothelial nitric-oxide synthase plays a role in BP regulation by modulating vascular tone through the production of nitric oxide in the vascular endothelium.

Interestingly, Wang et al. reported that ascorbic acid prevented the development of HTN in rat offspring prenatally exposed to lipopolysaccharide (LPS) (71). LPS exposure induced histone H3 acetylation in the ACE1 promoter region, resulting in increased ACE1 gene expression and HTN in rat offspring. Prenatal treatment with ascorbic acid, however, reversed the histone modification and led to less ACE1 gene expression (71). These findings suggest potential targets for novel antihypertensive therapies that can prevent or treat HTN early in life.

### Non-Coding RNAs

Non-coding RNAs are increasingly recognized as crucial regulators of gene expression and may influence cell-specificity of gene expression (61). Among non-coding RNAs, miRNAs have been the most widely studied in association with HTN. miRNAs are small non-coding RNAs, approximately 22 nucleotides in length, that silence mRNA expression through mRNA degradation or interference of mRNA translation (72). miRNAs have been reported to modulate BP through various mechanisms. One such mechanism is through the renin–angiotensin system pathway. In human kidneys, hsa-miR-663 was observed to regulate the mRNA levels of renin (*REN*) and apolipoprotein E (*APOE*) by binding to their 3′ untranslated regions (73). In addition, hsa-miR-181a was also found to regulate the mRNA expression of *REN* and apoptosis-inducing factor mitochondrion-associated 1 (*AIFM1*). Both miRNAs were downregulated in HTN, leading to increased expression of renin mRNA (73).

Studies are also ongoing for potential treatments for HTN based on epigenetic modifications. Mutations in mitochondrial DNA (mtDNA) have been linked to the development of HTN, proposedly through the action of reactive oxygen species (74). Consistent with these findings, Li et al. observed a decrease in mtDNA-encoded cytochrome *b* (mt-Cytb) and corresponding increase in reactive oxygen species in hypertensive rats (75). Interestingly, they found that when miR21, an miRNA that was found in higher levels in the hypertensive rats compared with controls, was injected into the hypertensive rats *via* a recombinant adeno-associated virus, there was an increase in mt-Cytb levels and lower BPs (75). The authors hypothesized that miR21 plays a compensatory role in HTN. Studies such as these are promising for the development of novel therapies that utilize epigenetic mechanisms, such as miRNAs, to treat HTN.

## PHARMACOGENOMICS AND HTN

Pharmacogenomics refers to the study of genes that can affect a patient's response to drugs. The goal of pharmacogenomics is to develop tailored medications and doses that take into account the differences in each individual's response to drugs. Extensive research has been performed on the genetic aspect of responses to antihypertensive medication, which include drug interaction with the target sites, drug transport, and metabolism. The Clinical Pharmacogenetics Implementation Consortium (CPIC), formed in 2009, establishes guidelines that aid with application of results from pharmacogenetic studies to actionable prescription of drugs (76). However, due to inconsistent results across studies and therefore insufficient evidence, there are no CPIC guidelines to date for antihypertensive medications (77, 78).

The International Consortium for Antihypertensive Pharmacogenomics Studies was established in 2012 to facilitate research of genetic variants that are responsible for interpatient variability in responses to antihypertensive medications (http://icaps-htn.org). To date, the most consistently reproducible pharmacogenomic data have been based on β-blockers and thiazide diuretics (78). Three genes, *ADRB1*, *NEDD4L*, and *YEATS4*, have been consistently linked with responses to antihypertensive drugs in various studies. The *ADRB1* gene encodes the β-1 adrenergic receptor, which is targeted by the β-blockers. Common SNPs in the *ADRB1* gene include the variants Ser49Gly (rs1801252) and Arg389Gly (rs1801253) (78). Patients who were homozygous for Arg389 and patients possessing the Ser49Arg389/Ser49Arg389 diplotype were reported to have a greater reduction in BP with metoprolol compared with those who were Gly allele carriers and those who had the Gly49Arg389/Ser49Gly389 diplotype, respectively (79, 80).

*NEDD4L* encodes a protein that downregulates the expression of ENaC in the distal nephron, thereby regulating sodium reabsorption in the kidneys (81). Several studies have shown that the more common G allele of rs4149601, located within the *NEDD4L* gene, is linked to greater systolic and diastolic BP reduction in response to thiazide diuretics (82, 83). These findings are

consistent with the role of *NEDD4L* in reducing tubular sodium reabsorption.

Single-nucleotide polymorphisms (rs317689/rs315135/rs7297610) close to the *YEATS4* gene have also been associated with varying responses to thiazide diuretics (84). The *YEATS4* gene encodes a protein, GAS41, which is involved in regulation of cellular proliferation (78). Through GWAS, the rs317689/rs315135/rs7297610 haplotype was found to be significantly associated with diastolic BP response to hydrochlorothiazide (HCTZ) in African-Americans. The ATC haplotype was linked to a good response to HCTZ, while the ACT and the ATT haplotypes were associated with a poor response to HCTZ (84). The data on gene polymorphisms affecting responses to calcium channel blockers, ACE inhibitors, and angiotensin II receptor blockers are conflicting, and no candidate gene has shown consistent results (85, 86). A summary of recent pharmacogenomic findings on responses to antihypertensive medications is provided in **Table 3**.

## GENETICS OF ESSENTIAL HTN IN CHILDREN

Pediatric genetic studies on HTN are scarce in comparison to adult studies and are often limited by small sample size. A recent study investigated the parental effects of 33 SNPs previously identified by GWAS on the BP of young offspring (53). Based on 1,525 subjects from the Family Atherosclerosis Monitoring In early life study, significant parental effects, albeit small, were reported for the SNPs rs11191548 (*CYP17A1*) and rs17367504 (*MTHFR*) (53). The paternal genotype of rs11191548 was found to be associated with elevated systolic and diastolic BP among offspring, whereas there was no association with the maternal genotype. Both the maternal and paternal genotypes of rs17367504 were associated with elevated systolic and diastolic BP among offspring. This study also observed that the SNP rs1378942 (*CSK*) demonstrated an association with systolic BP from birth to 5 years of age (53).

**TABLE 3** | Genes associated with responses to antihypertensive medications [modified from Burrello et al. (14)].

| Associated gene (single-nucleotide polymorphisms) | Antihypertensive drug response | Reference |
|---|---|---|
| *ADRB1* (rs1801252, rs1801253) | Greater response to metoprolol | Liu et al. (80); Johnson et al. (79) |
| *ADRB1* (rs 1801253) | Greater reduction in diastolic blood pressure (DBP) with carvedilol | Si et al. (87) |
| *ADRB2* (rs2053044) | Reached target mean arterial pressure faster with ramipril | Anthony et al. (88) |
| *NEDD4L* (rs4149601) | Greater systolic blood pressure (SBP) and DBP reduction in response to thiazide diuretics | Svensson-Färbom et al. (82); McDonough et al. (83) |
| *CAMK1D* (rs10752271) | Greater reduction in SBP in response to losartan | Frau et al. (89) |
| *YEATS4* (rs317689, rs315135, rs7297610) | ATC haplotype associated with greater reduction in DBP with thiazide diuretics | Turner et al. (84) |

*CSK* is a tyrosine kinase that plays a role in actin remodeling, which in turn has been shown to affect constriction of the arterial endothelium in murine newborns (54). Although limited by sample size, this was the first study to investigate the effect of parental SNPs on young offspring, and SNPs that affect BP in the early years of life.

In another study, the polymorphism T585C of the Y2 receptor (Y2R) gene was reported to be associated with systolic and diastolic BPs in obese children (90). Y2R is a receptor for neuropeptide Y, which is a potent constrictor of vascular smooth muscle cells. Y2R has also been observed to regulate neurogenic vasoconstriction in spontaneously hypertensive rats (91). Obese children homozygous for the T585 allele in *Y2R* showed significantly lower systolic and diastolic BPs compared with heterozygotes and C allele homozygotes (90).

Genetic predisposition for BP elevation spanning from childhood to adulthood was assessed in a longitudinal study that employed a combined genetic risk score formulated from 13 SNPs previously associated with HTN in adults (92). Subjects with a higher risk score at the age of 9 years had significantly higher diastolic BPs than subjects with a lower risk score. These subjects also had a higher risk for HTN in adulthood (92). Although the effect size was small ($\beta = 0.68$ mmHg) (92), this study provides a method for detecting individuals with a genetic predisposition for HTN early in childhood and may be used to identify those patients in which early preventive measures can be implemented.

The association between SNPs and BP in certain ethnic pediatric populations has also been reported in several recent studies. In a study of Chinese children, rs17249754 (*ATP2B1*) was found to be significantly associated with an increased risk for HTN (93). This polymorphism has also been previously linked to HTN in adults. *ATP2B1* encodes a calcium-transporting ATPase that modulates cellular calcium levels in the vascular endothelium, thereby regulating the contraction of vascular smooth muscle cells (94). In a study of Lithuanian children, the insertion/deletion (I/D) polymorphism (rs4340) for *ACE* was found to have a gender-specific association with BP (95). Boys with the *ACE I/D* and *ACE I/D + D/D* genotype had significantly increased odds for developing HTN (95), consistent with previous findings that adults homozygous for the D allele have higher plasma ACE concentrations than heterozygotes (96). Similar to these findings, the D-allele of the *ACE I/D* polymorphism was also associated with HTN in obese Brazilian boys (97).

Childhood HTN is a significant risk factor for HTN and cardiovascular disease in adulthood (98–100). Therefore, pediatric studies that identify genetic risk factors and modifiable epigenetic factors for HTN are further needed to formulate preventive strategies that can reduce childhood HTN, and therefore morbidity and mortality later in life. Moreover, drug pharmacokinetics differ between children and adults (101). Pediatric-based pharmacogenomic research would be beneficial in identifying the genes responsible for each child's response to antihypertensive drugs. Antihypertensive drugs have multiple side effects that can have a negative impact on a child's quality of life. Identifying the genes that predispose a child to poor or adverse drug responses would be beneficial in avoiding complications and optimizing therapeutic responses.

## CONCLUSION

Hypertension results from a complex interplay of genetic, epigenetic, and environmental factors. Due to this multifactorial interaction, elucidating single, specific genetic factors that contribute to the development of HTN has been challenging. Nevertheless, novel gene mutations and epigenetic factors causing BP variability continue to be discovered and have enhanced our understanding of BP modulation and the genetic programming of HTN. Interpatient variability in response to antihypertensive medication is well established, and the field of pharmacogenomics promises to provide guidelines for precision medicine and individually tailored antihypertensive regimens that would improve medication efficacy. The majority of genetic studies on HTN to date have been focused on adults, and there are currently few studies that have been conducted in the pediatric population. In view of the prevalence of HTN in the pediatric population, more studies on the genetic risk factors in this population are needed to enhance our understanding of the etiology of childhood HTN and to provide better preventive and therapeutic strategies for the future.

## AUTHOR CONTRIBUTIONS

S-YA and CG contributed to the conception and writing of the manuscript. Both authors provided their final approval and agreed to be accountable for all aspects of the manuscript.

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# Developmental Origins and Nephron Endowment in Hypertension

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Primary hypertension continues to be one of the main risk factors for cardiovascular disease worldwide. A stable intrauterine environment is critical for the future development and health of the fetus. The developing kidney has been found to be especially vulnerable during this time period, and epidemiological studies have demonstrated that an adverse *in utero* environment is associated with an increased risk of hypertension and chronic kidney disease. Macro- and micronutrient deficiencies as well as exposure to tobacco, alcohol, and certain medications during gestation have been shown to negatively impact nephrogenesis and reduce one's nephron number. In 1988, Brenner et al. put forth the controversial hypothesis that a reduced nephron complement is a risk factor for hypertension and chronic kidney disease in adulthood. Since then numerous animal and human studies have confirmed this relationship demonstrating that there is an inverse association between blood pressure and nephron number. As our understanding of the developmental programming of hypertension and other non-communicable diseases improves, more effective preventive health measures can be developed in the future.

**Keywords: hypertension, nephron, fetal origins hypothesis, low birth weight, blood pressure**

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## INTRODUCTION

Primary hypertension is one of the leading risk factors for morbidity and mortality in the world, and it has been designated as the primary risk factor for the global disease burden (1, 2). Approximately 75 million adults have been diagnosed with hypertension in the United States, and among industrialized countries, it affects 25–35% of individuals globally (3). It is predicted that the number of individuals affected by hypertension will continue to rise and, by 2025, approximately 1.5 billion individuals will be affected (4). Hypertension continues to be the main risk factor for cardiovascular disease (CVD), and current literature states that there is a strong, positive correlation between blood pressure and risk of CVD (5). Although the pathogenesis of hypertension remains unclear, it is evident that the kidneys play a significant role in its development.

Recently, attention has been paid to the contribution of the intrauterine environment to the development of chronic and non-communicable diseases. Epidemiological studies have demonstrated that a poor intrauterine environment is associated with an increased risk of hypertension, chronic kidney disease, and diabetes (6–9). The developing kidney, in particular, has been found to be susceptible to an unstable fetal environment (10). Although multiple factors contribute to the genesis of hypertension, reduced nephron number has been attributed to be a significant contributor (11). In this review, we discuss the various factors that influence nephron endowment. We also highlight key findings on the relationship between nephron number and blood pressure in the pediatric and adult populations.

## NEPHRON ENDOWMENT

Nephrogenesis begins at the gestation age of 9 weeks and is approximately complete by the 36th week (12–14). It is characterized by reciprocal, inductive interactions between the ureteric bud and the metanephric mesenchyme. The metanephric mesenchyme initiates ureteric branching morphogenesis *via* the secretion of growth factors, resulting in the development of the collecting duct system (15–19). Similarly, the branching ureteric bud induces the conversion of mesenchyme to epithelium in the adjacent metanephric mesenchymal cells. These cells are induced to form renal vesicles, which will further differentiate into the comma-shaped bodies and s-shaped bodies ultimately forming a mature nephron. Upon completion of this process, no new nephrons are formed. Therefore, by the end of nephrogenesis, an individual's entire nephron complement is established (10).

Among humans, the average number of nephrons per kidney is approximately 1,000,000, but there is a significant amount of variation within the human population. Nephron number can range from as low as 200,000 to as high as 2.7 million (20, 21). This variation in nephron number demonstrates the plasticity of the developing kidney, and the significant role one's environment plays in determining one's final nephron count.

## DETERMINANTS OF NEPHRON NUMBER

Nephron endowment arises from the complex interplay among one's genetic blueprint, perinatal events, and environmental exposures (**Figure 1**) (20, 22). A stable intrauterine environment is essential for proper renal organogenesis, and it is becoming more and more evident that the *in utero* environment plays a crucial role in the future development and health of the offspring (10). The following section further describes the relationship among these factors and nephron endowment.

### Birth Weight

Birth weight has been identified as the primary determinant of nephron number (23). Low birth weight due to intrauterine growth restriction or prematurity has been shown to be associated with a reduced nephron complement. When evaluating the coronal sections of kidneys from deceased neonates, Manalich et al. discovered that neonates with lower birth weights (<2,500 g) had significantly fewer glomeruli than those with normal birth weights. In addition, they observed a direct relationship between birth weight and glomerular number and an inverse relationship between glomerular volume and the number of glomeruli. This suggests that individuals with low birth weights are more likely to have fewer, larger glomeruli (24). Similarly, Hughson et al. detected a direct association between birth weight and glomerular number among Caucasian and African-American infants, children, and adults. A 1 kg increase in birth weight was found to be associated with an increase in 257,426 glomeruli. In addition, low birth weight was found to a predictor for fewer glomeruli in their study (23).

In addition, racial and ethnic populations with a high prevalence of low birth weight have been found to have fewer nephrons or smaller kidneys (25–27). Babies born to Australian Aborigines are twice as likely to be of low birth weight compared to non-Aborigines. Hoy et al. discovered that Australian Aboriginal subjects had approximately 404,000 fewer glomeruli than non-Aboriginals and a significantly larger mean glomerular volume (25). They also observed a strong association between adult height and glomerular number. These findings further corroborate the

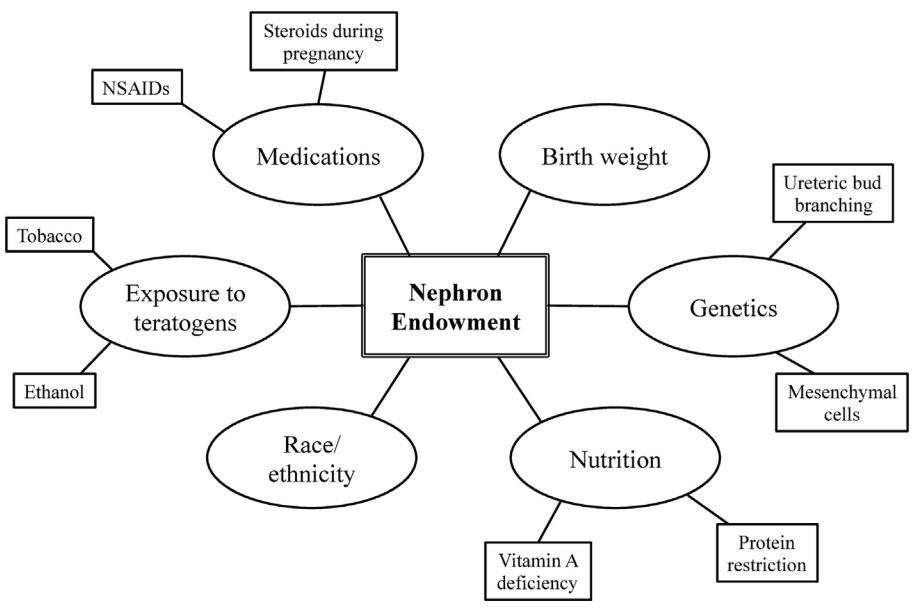


**FIGURE 1** | Factors influencing nephron endowment.

relationship between birth weight and nephron number within this population, as birth weight is a strong predictor of adult height.

## Genetic Factors

Numerous mouse models have demonstrated that inadequate ureteric bud branching results in decreased nephron number. Null mutations in genes implicated include those regulating the formation and function of: epidermal growth factors, fibroblast growth factors (e.g., *fgf7* and *fgf10*), glial cell-derived neurotrophic factor (*gdnf*, *c-ret*, and *gfrα*), hepatocyte growth factor (e.g., *hgf* and *c-met*), transforming growth factor β (e.g., *tgfβ2* and *tgfβ3*), and signal transduction proteins from the Wnt family (28–32). For purposes of this review, we have chosen to highlight two genes whose physiological implications have been demonstrated through studies on human subjects.

The Six2 gene has emerged as a key player in kidney development. It is expressed throughout renal organogenesis in undifferentiated mesenchymal cells and encodes a homeodomain transcriptional regulator (33). Its continual expression is needed to maintain the nephron progenitor population (34, 35). Kobayashi et al. demonstrated that Six2+ expressing cap mesenchymal cells are multipotent nephron progenitors that give rise to the multiple domains of the nephron (34). Its inactivation results in the reduction of the number of progenitor cells, and these cells autonomously maintain its own cell population (34, 35). The knock out of the Six2 gene in mice models was found to result in the formation of ectopic renal vesicles (35). Furthermore, Weber et al. discovered mutations within the Six2 gene among a subset of patients with renal hypodysplasia (36). Therefore, mutations, which affect the Six2 gene product, can adversely affect nephrogenesis.

Interestingly, genetic variants that increase nephron number have also been identified. El Kares et al. identified a variant of the ALDH1A gene, rs7169289(G), that is associated with an increased total kidney volume in newborns when adjusting for body surface area. The ALDH1A gene is involved in the metabolism of retinoic acid, and infants who were homozygous for this variant were found to have higher umbilical cord blood levels of retinoic acid (37).

## Nutrition

Maternal nutrition plays an essential role in the development of the fetus. The developing kidney is especially vulnerable to the effects of a poor maternal diet, and maternal malnutrition during pregnancy has often been proven to be associated with suboptimal renal phenotypes among her offspring (10). Macro- and micronutrient deficiencies as well as restricted caloric intake have been demonstrated to impair kidney development during gestation (10, 22).

Protein restriction during gestation significantly reduces nephron number (38–41). Woods et al. discovered that male protein-restricted rats had 25% less nephrons than protein replete controls as well as a higher mean arterial blood pressure in adulthood. Renal hyperfiltration was also observed among subjects, as protein-restricted offspring had a higher individual nephron glomerular filtration rate. Interestingly, the subjects' intrarenal renin mRNA, renin concentration, and immunostaining for renin were reduced during nephrogenesis. Subsequently, their intrarenal angiotensinogen II levels were also reduced throughout nephron development. These results imply that RAS has an additional role in the regulation of blood pressure. In addition to maintaining blood pressure in adulthood, it influences the final nephron number during nephrogenesis. Therefore, the RAS system may act as a mediator in the relationship between protein restriction and nephron number (40). A high protein diet, however, was not found to influence nephron endowment (42).

Micronutrients also significantly impact renal organogenesis (10, 22). Gilbert proposed that vitamin A is largely responsible for significant variations in nephron number among humans. Vitamin A serves as a ligand to c-RET, c-ret tyrosine kinase receptor (43). This receptor plays a critical role in early kidney development as it is involved in the initiation of ureteric branching. Maternal iron and zinc deficiencies have also been found to reduce nephron number and increase systolic blood pressure in adult offspring. However, the mechanism behind these associations is less understood (10). Overall, there are a variety of nutrient deficiencies that result in the same structural renal phenotype. Therefore, a reduced nephron number may serve as an adaptive response from the developing kidney during times of environmental stress (10).

## Teratogens

The detrimental effects of chronic alcohol exposure to the fetus during pregnancy have been well documented. However, the effects of acute prenatal alcohol exposure are less understood, especially its influence on the developing kidney. Gray et al. investigated the effects of acute prenatal ethanol exposure on nephron endowment in rats. Either ethanol or saline was administered to Sprague-Dawley rats on embryonic days 13.5 (E13.5) and 14.5 (E14.5). Ethanol exposed rodents were found to have a 10–20% reduction in nephron number as well as a higher mean arterial blood pressure. In addition, E15.5 rats were found to have a reduced gene expression of significant regulators of ureteric branching morphogenesis (GDNF, FGF7, Wnt11, TGFβ2, and TGFβ3). Fewer ureteric branch points and tips were also found in embryonic kidneys that were cultured in media containing ethanol (44).

Tobacco exposure is another established teratogen, which has been demonstrated to be negatively associated with birth weight and positively associated with blood pressure (45, 46). Taal et al. conducted a population-based prospective cohort study of 1,072 mothers and children to investigate the association between prenatal cigarette exposure and kidney volume. Mothers who only smoked during the first trimester and those who smoked throughout their pregnancy were followed. A consistent relationship between smoke exposure and kidney volume was not observed among the offspring of mothers who smoked solely during the first trimester. However, a dose-dependent relationship between kidney volume and tobacco exposure was observed among the offspring whose mothers smoked throughout their pregnancy. Those who smoked more than 10 cigarettes a day had a smaller total fetal kidney volume than those who smoked less

than five cigarettes a day (47). These results once again imply the importance of a stable intrauterine environment as disturbances may predispose an individual to cardiovascular and renal diseases.

### Medication

Elevated levels of maternal corticosteroids during pregnancy have been shown to be associated with a low nephron complement and higher blood pressure among her offspring (22). Interestingly, both the duration and timing of the exposure determine the severity of the phenotype and only 2 days of exposure is needed to produce a nephron deficit. Administration of dexamethasone (DEX), a synthetic glucocorticoid, during embryonic day E15/16 or E17/E18 was found to decrease glomerular number and increase blood pressure in rat models. Similarly, DEX exposure during day E19/E20 or E26-28 was also found to result in hypertensive sheep offspring with a nephron deficit. However, administration of DEX before or after these time periods was not found to affect glomerular number or blood pressure. The time periods when animals were most susceptible to DEX were during times of kidney development, specifically during ureteric branching morphogenesis. Singh et al. proposed that DEX reduces nephron number by inhibiting/slowing ureteric branching. They reported that DEX exposure decreased the expression of GDNF (a promoter of ureteric branching) and increased the expression of inhibitors, BMP-4 and TGF-β1 both *in vitro* and *in vivo* (48). Ureteric branching morphogenesis is believed to be a significant process in establishing the final nephron complement as each ureteric tip induces the formation of new nephrons. Therefore, by inhibiting ureteric branching, DEX indirectly reduces nephron number (48).

Exposure to non-steroidal anti-inflammatory drugs has been shown to have variable effects on one's nephron number (22). Rodents that were exposed to cyclooxygenase-2 inhibitors from gestation to 3 weeks postbirth were found to have a significantly reduced glomerular size. Interestingly, if exposure occurred solely during gestation, no effect on glomerular size was observed (49).

## DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

One of the initial proponents of the fetal origins of disease was Dr. David Barker. In the 1980s, Barker and colleagues discovered an inverse relationship between birth weight and coronary artery disease mortality rates in a cohort of men and women born in Hertfordshire, United Kingdom. They observed a twofold increase in mortality rates when comparing individuals with the lowest birth weight with those with the highest birth weight (50, 51). Barker eventually proposed that fetal undernutrition during middle to late gestation "programs" coronary artery disease in adulthood (52). Future epidemiological studies supported the Barker hypothesis, demonstrating the importance of one's intrauterine environment in determining one's future health (6–9). These findings further shed light on the non-hereditary component of chronic diseases.

The theory of "developmental programming" or the "developmental origins of health and disease," states that environmental influences during sensitive periods of development can result in permanent alterations of function and structure of an organism (53). In order to increase its chances of surviving, the fetus may undergo structural and functional changes during gestation at the expense of its future health. Therefore, an adverse intrauterine environment can predispose an individual to an increased risk of hypertension and cardiovascular or renal disease (6–9). The developing kidney has been shown to be especially vulnerable to a suboptimal *in utero* environment (10). As described previously, in addition to one genetic disposition, macro- and micronutrient deficiencies and exposure to teratogens and certain medications during gestation have been found to reduce one's nephron endowment (10, 22, 44, 48). Interestingly, each of these different environmental signals elicits a similar renal phenotype in the offspring.

In 1988, Brenner et al. put forth the hypothesis that a low nephron number is a risk factor for adult hypertension (**Figure 2**). They proposed that a reduction in the total filtration surface area of the kidneys is associated with a compensatory increase in the single nephron glomerular filtration rate. In response to a reduced nephron complement, adaptive structural changes occur within the nephron including glomerular and tubular enlargement and an increase in the number of glomerular capillaries. Consequently, the afferent arteriole dilates while the efferent arteriole constricts resulting in an increase in the glomerular capillary pressure. This reduction in the afferent arteriolar resistance allows for an increased transmittance of systemic blood pressure into the glomerulus. Simultaneously, other physiological changes occur that also contribute to the development of hypertension including increased salt reabsorption, higher volume strokes and cardiac output and resetting of the pressure-natriuresis curve. Pathological changes such as podocyte detachment and tuft adhesion to Bowman's capsule have been noted in sclerosed kidneys compensating for hyperfiltration (e.g., secondary

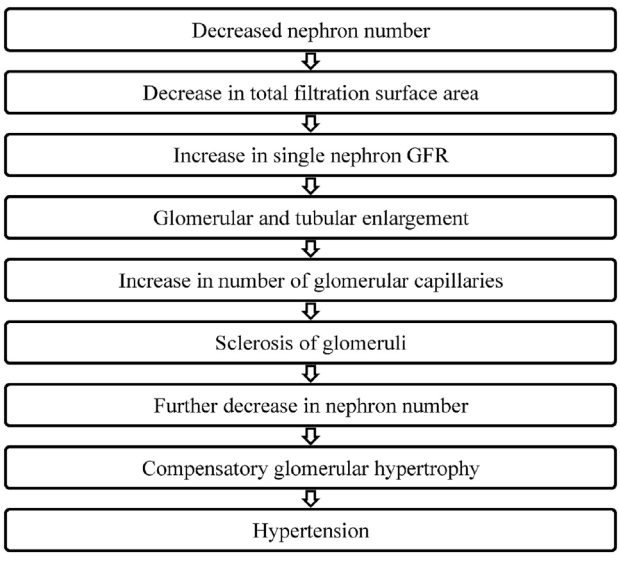


**FIGURE 2** | How does nephron number lead to hypertension?

to vesicoureteral reflux) (54). Over time, this sclerosis of the glomeruli fuels a vicious cycle resulting in a decreased nephron number, the compensatory glomerular hypertrophy, and the progressive hypertension and chronic kidney disease (55–57).

## NEPHRON NUMBER AND HYPERTENSION

Since initially hypothesized over 30 years ago, there have been a number of animal and human studies that have sought to determine the relationship between nephron endowment and hypertension.

### Animal Studies

Through animal studies, it is becoming increasingly clear that a relationship exists between nephron number and hypertension. A mouse model of prematurity found that those delivered 1 and 2 days early had 17.4 and 23.6% fewer nephrons, respectively, compared to full-term mice, and the premature mice subsequently developed hypertension (58). In addition, a number of genetic knock out mice models associated with lower nephron number have demonstrated an inverse association with blood pressure (59–61).

### Low Birth Weight and Nephron Number in Humans

Human epidemiological studies have used birth weight as an indicator of fetal nutrition status and therefore a surrogate for lower nephron endowment. Systematic reviews and meta-analyses of the literature have consistently shown an inverse relationship between birth weight and blood pressure. Law et al. reviewed 34 cohort studies published before 1996. After adjustment for body mass index, regression coefficients of birth weight indicated a negative association with systolic blood pressure in 26 studies, indicating a 2–3 mmHg/kg reduction in systolic blood pressure in children and 2–4 mmHg/kg reduction in adults with increasing birth weight (62). In a review by Huxley et al. of 45 pediatric and adult studies published between 1996 and 2000, the majority (33 studies) reported a negative association between birth weight and systolic blood pressure. In aggregate, an 1 kg increase in birth weight was associated with an 1–2 mmHg/kg decrease in systolic blood pressure (63). A review by Adair et al. of 2000–2005 publications of adult studies remains consistent with the earlier ones. Of the 28 cohort studies, 25 studies found an inverse association; however, not all were adjusted for BMI (64). More recently, a meta-analysis of 27 studies conducted between 1995 and 2012 found that low birth weight (<2,500 g) compared with birth weight greater than 2,500 g was associated with an increased risk of hypertension (odds ratio 1.21; 95% confidence interval 1.13, 1.30) (65).

The relationship between birth weight and blood pressure in childhood is more complicated, and studies published since 2000 have shown inconsistent results muddied by poorly powered studies focusing on specific populations. There is also some evidence that the inverse relationship between blood pressure and birth weight becomes more pronounced as the age of the study population increases, although this finding is weak and may not be statistically significant (66). Studies of adolescents show conflicting results, and in neonates, some studies reported a positive relationship between blood pressure and birth weight (62). Rahiala et al. showed that birth weight was not an independent determinant of blood pressure in 100 children in Finland using ambulatory blood pressure monitoring (67). However, four other studies with larger sample sizes supported the inverse relationship of birth weight and ambulatory blood pressure in children (68–71). Though low birth weight does appear to be associated with hypertension, the physiological and molecular mechanisms establishing causality remain to be elucidated.

### Impact of Ethnic and Racial Factors

There is a significantly higher prevalence of hypertension in African-Americans, which is likely multifactorial in etiology. African-Americans are also at higher risk for being low birth weight. This suggests that being low birth weight could be one of the factors implicated in predisposing African-Americans to higher rates in hypertension later in life (23).

Since most of the studies in this area focused on Caucasians, there is little published on the African-American population. Hulman et al. evaluated 137 urban African-American adults and found no relationship between birth weight and adult blood pressure (72). Donker et al. looked at a biracial sample of 1,446 children aged 7–11 years and found evidence that low birth weight is a determinate of high blood pressure only in African-American males. However, the association was lost when multivariate analyses were done (73). A study by Rostand et al. analyzed 262 Caucasian and African-American 5-year-old children. An inverse relation was found for Caucasian children, but, surprisingly, a positive relationship was found for African-American children (74). However, an inverse relationship between birth weight and blood pressure was found in the longitudinal Bogolusa Heart Study and there were no racial differences found (75).

Interestingly, hypertension is also highly prevalent among Australian Aboriginals and it appears that a reduced nephron complement mediates the relationship between low birth weight and hypertension within this population (25). Hoy et al. reported that Aboriginals were endowed with fewer and larger glomeruli than non-Aborigines. In addition, as expected, Aborigines with a history of hypertension had significantly fewer glomeruli than those who did not. When evaluating the relationship between kidney volume and blood pressure within this population, the investigators reported that renal volume was inversely associated with blood pressure in both Aboriginal children and adults.

### Postnatal Influences on Nephron Number

Low birth weight has been shown to impact the nephron number at birth; however, numerous factors affect nephron number throughout one's lifetime. Environmental factors such as weight gain and aging later change nephron number and therefore risk (76, 77). However, studies evaluating these factors have been difficult to conduct in humans, as there are no accurate methods accounting for nephron number that leave the kidney undamaged.

Nephrons are hypertrophied atrophy sooner, therefore decreasing the nephron number even more so (78). Though it is commonly said that reduction in glomerular number occurs naturally with

age, far greater reduction has been found to occur in hypertensive patients (79). Keller et al. found that the mean glomerular number for hypertensive patients was half that of the normotensive patients (11), though the mean glomerular volume was 133% greater. In this same study, kidney samples were also analyzed for histological evidence of hypertension. Even when including glomeruli obliterated due to sclerosis, hypertensive patients had significantly lower glomerular number than normotensive patients.

## CONCLUSION

There is an increasing body of literature demonstrating the relationship between nephron number and hypertension. These studies show that there is an inverse relationship between nephron endowment and hypertension. As this relationship is established, factors that contribute to determining nephron number are being elucidated. Genetics clearly plays a role in nephron endowment, one that possibly explains racial differences in nephron number at birth. Environmental factors such as birth weight, body size, and age also have an impact. Having a way to assess for life-long risk of renal and CVD could be instrumental in initiating preventive health measures earlier in life. Like genetics, low birth weight is a predetermined risk factor that could be utilized for risk stratification and thus early initiation of preventive health measures. Recent advances in accurate and precise estimates of glomerular number will improve our understanding of the factors contributing to nephron endowment and its implications for future health.

## AUTHOR CONTRIBUTIONS

SG, AT, and CS contributed equally to the writing of this manuscript.

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REVIEW
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# Obesity-Related Hypertension in Children

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Obesity and hypertension have both been on the rise in children. Each is associated with increased cardiovascular disease risk and both track into adulthood, increasing the prevalence of heart disease and related morbidity and mortality. All children should be screened for hypertension, but children with comorbid obesity may not only particularly benefit from the screening but may also prove the most challenging to screen. Increased arm circumference and conical arm shape are particularly problematic when attempting to obtain an accurate blood pressure (BP) measurement. This review focuses on the unique aspects of hypertension evaluation and management in the child with comorbid obesity. Specific traditional and non-traditional risk factors that may contribute to elevated BP in children with obesity are highlighted. Current proposed pathophysiologic mechanisms by which obesity may contribute to elevated BP and hypertension is reviewed, with focus on the role of the sympathetic nervous system and the renin–angiotensin–aldosterone system. This review also presents a targeted treatment approach to children with obesity-related hypertension, providing evidence for the recommended therapeutic lifestyle change that should form the basis of any antihypertensive treatment plan in this population of at-risk children. Advantages of specific pharmacologic agents in the treatment of obesity-related hypertension are also reviewed.

**Keywords: pediatrics, blood pressure, cardiovascular disease, adiposity, adipocyte, adipose tissue dysfunction**

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## INTRODUCTION

Since 1980, the prevalence of obesity among children and adolescents has almost tripled. Current estimates suggest that approximately 17% of children 2–19 years of age are obese. This percentage equates to 12.7 million children in the United States (1). These data are more striking when you include those who are overweight: 30%, or 25 million, US children are overweight/obese.

While these statistics are remarkable in their own right, the implications are particularly concerning. Children with obesity are at a significantly increased risk for cardiovascular disease (CVD): they have higher systolic and diastolic blood pressure (BP) and greater evidence of dyslipidemia and insulin resistance (2). In fact, 70% of obese children have at least one CVD risk factor, and 39% have two or more (3). These CVD risk factors, along with obesity, are not only associated with heart disease in childhood (i.e., atherosclerosis and left ventricular hypertrophy) but are associated with an increased prevalence of CVD risk factors in adulthood—which results in increased CVD morbidity and mortality (4–8).

**Abbreviations:** AAP, American Academy of Pediatrics; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; DASH, dietary approaches to stop hypertension; NHANES, National Health and Nutrition Examination Survey; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

These known associations and the now well recognized phenomenon of CVD risk factor tracking from childhood into adulthood has resulted in a greater emphasis on obesity prevention. In addition, the American Heart Association and the American Academy of Pediatrics (AAP) have emphasized the importance of primordial and primary prevention to achieve CVD risk reduction in youth (9, 10). An essential component of this strategy is regular screening for elevated BP and hypertension among children. Current guidelines recommend at least yearly BP measurements in all children 3 years of age and above. Any BP elevation should be confirmed with repeated measurements and the diagnosis of hypertension should be given to any child with a sustained elevation in his/her BP at or above the 95th percentile when measured by manual auscultation. All children with a diagnosis of hypertension should undergo evaluation for a secondary cause (11).

## EVALUATION OF THE CHILD WITH OBESITY AND HYPERTENSION

As introduced above, children with elevated BP should have their BP elevations confirmed with repeated measurements done by manual auscultation. Children with obesity can present unique challenges to BP measurement. For one, their arm size may be sufficiently large to require a BP cuff much bigger than would be expected by the labeling on the cuff (i.e., adult, large adult, thigh). Analyses using National Health and Nutrition Examination Survey (NHANES) data revealed that, based on measured mid-arm circumferences, some children as young as 3–5 years of age require an adult cuff, and starting at age 12 years some children require the use of a thigh cuff for proper BP measurement (12). Individuals with obesity also often have conically shaped arms, with a large circumference proximally that tapers to a much smaller circumference at the cubital fossa. The difference between the proximal and distal upper arm circumferences can be as large as 20 cm, with the average difference being 8.7 cm (13). Finally, while the mid-arm circumference of children with obesity is often larger than might be expected for age, their arm length is not different than would be expected. This leads to an arm length that is disproportionally short for the cuff required for the measured arm circumference. Often the appropriately sized cuff will overlay the cubital fossa, making BP measurement by manual auscultation difficult and raising the possibility of inaccurate measurements.

These challenges are particularly problematic because accurate BP measurement in the child with obesity is perhaps even more important than among those peers of normal or healthy weight. In children up to 20 years of age, obesity is defined as a body mass index (BMI) ≥ 95th age- and sex-specific percentile and overweight is defined as a BMI ≥ 85th percentile but <95th percentile. Severe obesity in children is defined as either a BMI ≥ 120% of the 95th percentile (corresponding to the 99th percentile BMI), or a BMI ≥ 35 kg/m$^2$ (corresponding to the cutpoint of Class II obesity in adults), whichever is lower. After age 20 years, adult cutpoints for overweight and obesity apply (BMI between 25 and 30 kg/m$^2$ and BMI ≥30 kg/m$^2$, respectively). Adult studies have demonstrated that the risk of hypertension increases substantially with increasing BMI, with the odds of hypertension as great as 4.8 among adults with Class III obesity (BMI ≥40 kg/m$^2$) when compared to adults with a normal BMI (14). Obesity is also associated with resistant hypertension: hypertensive adults with Class III obesity had a 30% lower odds [OR 0.7, 95% confidence interval (CI) 0.5–0.9] of achieving a BP < 140/90 compared to those with a normal BMI (15).

Once a child with obesity has confirmed hypertension, he/she should undergo an evaluation to investigate for secondary causes of hypertension and screen for CVD risk factors. This evaluation should include the following (11):

| Evaluation | Unique aspects to obesity |
|---|---|
| Detailed history | • Sleep history<br>  ○ Daytime somnolence<br>  ○ Snoring<br>  ○ Witnessed apneic events<br>• Diet history<br>  ○ Sugar-sweetened beverage intake<br>  ○ Fiber intake<br>  ○ Total calories consumed<br>  ○ Timing and frequency of meals<br>• Physical activity<br>  ○ Amount and intensity<br>  ○ Musculoskeletal pain (which might impact ability to be active)<br>• Psychosocial history<br>  ○ Depression<br>  ○ Anxiety |
| Detailed physical exam | • Anthropometrics<br>  ○ Body mass index<br>  ○ Waist circumference<br>• Skin exam<br>  ○ Acanthosis nigricans<br>  ○ Hirsutism<br>  ○ Striae<br>• Abdominal exam<br>  ○ Hepatomegaly |
| Laboratory assessment | • Fasting lipids<br>• Fasting glucose and insulin<br>• Hemoglobin A1c<br>• Aspartate transaminase and alanine transaminase |

Tests to consider, particularly in children with obesity hypertension:

| Evaluation | Unique aspect to obesity |
|---|---|
| Polysomnography | Obstructive sleep apnea |
| Toxicology screen | Depression and anxiety are increased in obese children, leading to increased risk for illicit substances |

If a secondary cause is not determined after the initial evaluation in an older child or a child with a BP close to the 95th percentile, additional evaluation may not be warranted. One may then consider a diagnosis of primary or obesity-related hypertension.

## ROLE OF ADIPOSITY ON BP IN CHILDREN

As in adults, BMI influences BP in children. In a large cohort study of more than 100,000 children and adolescents followed for several years, those with obesity and severe obesity had higher BP at baseline and a greater odd of developing hypertension years later than those of lower BMI categories (16). The influence of adiposity on BP in children is also evident in the normative tables utilized by pediatric providers to diagnose hypertension. These tables were developed based on the first manual BP measurement obtained in children enrolled in any of 11 separate studies. The approximately 60,000 healthy children included in this database included children of normal weight as well as those with overweight or obesity. In fact, 21% of the included children had a BMI in the overweight or obese category. The impact of including these children is significant: when overweight and obese children are excluded from the normative table database, BP norms are lower by several mmHg across the board (17). The recently updated pediatric hypertension guidelines have addressed this issue by developing new tables based upon data from youth without overweight/obesity (18).

There are several possible pathophysiological pathways to explain why adiposity is associated with elevated BP and hypertension. The central tenet relates to the dysfunctional adipocyte and neurohormonal activation of the sympathetic nervous system (SNS). It is important to remember that the adipocyte not only serves as a storage depot for fat but is also an active endocrinological cell. Overweight and obesity is associated with a greater mass of adipose tissue, which includes adipocytes as well as pre-adipocytes, macrophages, and fibroblasts among other cell types (19). This tissue secretes various hormones and cytokines, known as adipokines, to maintain homeostasis. In the obese state, adipocytes are greater in number and size, and increasing amounts of adipokines are secreted. Over time, there is upregulation of pro-inflammatory adipokines. When the pro-inflammatory adipokines (leptin, resistin and IL-6, as examples) overwhelm the anti-inflammatory (i.e., adiponectin) adipokines, this imbalance leads to adipose tissue dysfunction and a chronic inflammatory state.

Many of these adipokines lead to an increase in SNS activity. Leptin, for example, has been shown to activate the SNS and studies in humans have demonstrated that Leptin deficiency is associated with lower SNS activity. This Leptin-mediated SNS activation appears to be dependent on the expression of leptin receptors on the proopiomelanocortin neurons in the brain (20). Mice without these receptors are resistant to the hypertensive effects of Leptin (21) and rats given alpha and beta blocker medications were similarly resistant to BP effects of intravenous infusion of Leptin (22).

Sympathetic nervous system activation can impact all organs, but in obesity appears to preferentially impact the renal vascular beds. Increasing BMI in humans is associated with increasing amounts of norepinephrine spill over in the kidneys, suggesting a link between obesity-related SNS activation and the neural release of renin (23). So, in addition to its direct vasoconstricting effects, increased SNS activity also leads to elevated BP and hypertension by increasing renin–angiotensin–aldosterone system (RAAS) activity. RAAS activity increases BP directly (angiotenisin II-mediated vasoconstriction and further SNS activation) and indirectly (angiotensin II- and aldosterone-mediated salt and water tubular reabsorption and ADH-mediated water retention). RAAS activity is further increased with increasing fat mass: adipocytes also secrete RAAS hormones and mineralocorticoid stimulating factors, with the relative contribution of these circulating levels related to the amount of adipose tissue present (24).

In the obese state, there is also increased inflammation with macrophages infiltrating the adipose tissue, and there is increased free fatty acid levels. Dyslipidemia, specifically elevated LDL-cholesterol and triglycerides and low HDL-cholesterol, is frequently comorbid with obesity. Elevated cholesterol is a known CVD risk factor, but its contribution to elevated BP and hypertension is complex. In addition to causing atherosclerosis, elevated LDL-cholesterol induces chronic inflammation, activates the SNS (25), and increases RAAS activity (26, 27). Among hypercholesterolemic individuals treated with statin therapy, SNS activity decreases along with a decrease in LDL-levels (28, 29).

Increased oxidative stress is another significant contributor to obesity-related hypertension. Oxidative stress also promotes SNS activation throughout the hypothalamus. Ultimately, with obesity full metabolic dysfunction occurs, leading to endothelial dysfunction, impaired pressure natriuresis, and poor vascular function, with hypertension the clinically identifiable outcome (30).

The increase in RAAS and SNS activation in obesity-related hypertension is important to recognize, as this has treatment implications for patients with obesity-related hypertension. As mentioned above, the serum levels of almost all components of RAAS are elevated in obesity, and in fact, the amount of adipose tissue present determines the relative amount of circulating angiotensinogen and angiotensin II (24). Weight loss, the first-line treatment for individuals with obesity-related hypertension, leads to a decrease in SNS activity which has direct effects on arterial pressure (decreased peripheral vasoconstriction), indirect effects on arterial pressure (improved pressure natriuresis resulting in lower intravascular volume), and a decrease in renin release from the kidney. In fact, menopausal women who successfully lost 5% of their body weight decreased their SBP by 7 mmHg and had lower angiotensinogen, renin, aldosterone, and angiotensin converting enzyme levels (31), providing experimental evidence for this effective means of treating obesity-related hypertension.

The important role of the SNS in obesity-related hypertension has been demonstrated in animal and human studies. In an experiment comparing the effect of weight gain on BP between dogs with and without bilateral renal denervation, both groups were fed the same high-fat diet and both had the same weight gain after 5 weeks. Despite this, only the dogs with intact renal innervation had higher BP and diminished urinary sodium excretion (32). In adults, adiposity is directly associated with increased muscle sympathetic nerve activity, which is considered a marker of overall sympathetic outflow (33). And, while invasive studies of SNS activity have not been done in children, children with

obesity-related hypertension have higher resting heart rates and increased BP variability than non-obese normotensive children (34). Both of these findings are considered indirect markers of SNS activity.

Finally, as with other visceral organs, in the obese state, the kidney can become fat encapsulated (19). When this occurs, there is increased renal interstitial fluid pressure and slower tubular flow rates which ultimately leads to increased sodium reabsorption and increased intravascular volume.

## TREATMENT APPROACH TO OBESITY-RELATED HYPERTENSION

The primary approach to all children with obesity-related hypertension should focus on the attainment of a healthy weight and achievement of a heart healthy lifestyle. The AAP recommends a staged approach to obesity treatment, with weight loss recommended for children 6 years of age and above when BMI is in the obese category and weight maintenance for growing children when BMI is in the overweight category (35). Weight loss is particularly important for children with obesity-related hypertension because it addresses the underlying etiology, it improves comorbidities and it reduces SNS activation, leading to lowering of BP. Several studies conducted in overweight and obese children ranging from 6 to 16 years of age have demonstrated the effectiveness of weight loss on lowering BP in children. These studies all incorporated diet, physical activity, education, and counseling and demonstrated a decrease in SBP from 6 to 16 mmHg over 5- to 12-month periods of intervention (36–38).

Dietary change is another important aspect of the lifestyle modifications needed to treat obesity-related hypertension. In 2011, the AAP published updated dietary recommendations for the treatment of hypertension (10). Regardless of stage of hypertension or etiology of hypertension, hypertensive children should institute the cardiovascular health integrated lifestyle diet and dietary approaches to stop hypertension (DASH) eating plan, which includes:

- increased intake of fresh vegetables, fruits, and low-fat dairy
- reduced carbohydrate, fat, and processed sugar intake
- limited/avoidance of sugar-sweetened beverages
- encouraged intake of foods with high dietary fiber content (age + 5 = number of grams/day up to 14 g/1000 kcal)

These dietary interventions have been shown to decrease BP in adults. In a randomized controlled feeding trial of adults with pre- or stage 1 hypertension, systolic BP was reduced by 6.6 (95% CI: 4.0–9.1) mmHg when following a DASH diet with a high sodium intake (compared to a usual diet with high sodium intake) and by 8.3 (95% CI: 6.6–10.0) mmHg when following a low-sodium diet in the setting of a Usual diet (compared to a high-sodium Usual diet) among those with hypertension. The degree of BP reduction was even greater when both interventions were implemented simultaneously: systolic BP was reduced by 11.5 (95% CI: 8.9–14.1) mmHg when a low sodium, DASH diet was followed (39) Hypertensive adolescents have also demonstrated decreased BP when enrolled in a clinic-based behavioral nutrition intervention emphasizing a DASH-type diet: systolic BP decreased by 10 mmHg and diastolic BP decreased by 6 mmHg among those prescribed a DASH-type diet (40).

Avoidance of sugar-sweetened beverages can also lead to weight loss among children and has been independently associated with BP reduction in adults. Two randomized controlled trials in children, one of overweight/obese children and another of normal-weight children, each demonstrated that elimination of sugar containing beverages leads to a reduction in weight and measures of adiposity (41, 42). In the PREMIER: Lifestyle Interventions for BP Control trial, a reduction of one 12-oz serving of sugar-sweetened beverages/day among adults over 18 months was associated with a reduction of systolic BP by 1.8 mmHg (95% CI: 1.2–2.4) and diastolic BP by 1.1 mmHg (95% CI: 0.7–1.4). These results remained significant even after adjusting for weight change (43).

There are no current guidelines regarding the degree of sodium reduction in children for the treatment of hypertension. Children should adhere to the Dietary Guidelines for Americans 2015–2020 (44) which states that children ≥14 years should limit daily sodium intake to <2,300 mg and younger children should limit sodium their sodium intake even more, with the upper tolerable limit for children 1–3 years of age being 1,500 mg. These guidelines also state broadly that pre-hypertensive and hypertensive individuals should reduce sodium intake to <1,500 mg. There is evidence to suggest that these recommendations may have a more significant impact on BP among children and adolescents who are overweight/obese than those who are not. In an NHANES study that included 6,235 children 8–18 years of age, 37% of whom were overweight or obese, usual sodium intake was estimated by multiple 24-h recalls. Notably, overall mean sodium intake was much greater than recommendations, with mean intake 3,387 mg/day. Overall, each 1 g of sodium intake per day was associated with an increased systolic BP SD score of 0.121 (95% CI 0.034–0.207) even after adjusting for age, sex, race, and energy intake. However, when the subjects were stratified by weight status, sodium intake was no longer associated with BP among the children of normal weight but it remained significantly associated with BP among the overweight/obese children (each 1 g sodium intake was associated with an increase in systolic BP SDS score of 0.197, 95% CI 0.036–0.357) (45). This differential effect of adiposity on the association of sodium intake and BP may be explained by the activation of the RAAS and SNS in the obese state as detailed above. Future studies need to explore this further.

Other essential components of the Heart Healthy Lifestyle include regular physical activity and a limit to sedentary activities. Specifically, children ≥5 years of age should partake in at least 1 h of moderate-to-vigorous exercise every day and all children should decrease their sedentary activities to <2 h per day. This may be difficult to achieve for children with obesity due to comorbidities such as arthritis, Blount's disease, slipped capital femoral epiphysis, spinal complications and acute fractures, all of which contribute to decreased mobility. Referral to physical

therapy can be helpful for some children as they work to achieve their physical fitness goals.

## ROLE OF PHARMACOLOGIC THERAPY

While all children with obesity-related hypertension should be prescribed therapeutic lifestyle changes, some children will also require an antihypertensive medication to adequately treat their hypertension. Children with a secondary etiology of hypertension, who are symptomatic, who have diabetes (type 1 or type 2), or who have end-organ damage such as left ventricular hypertrophy should all be prescribed an antihypertensive medication. In addition, children with persistent hypertension after 6–12 months of instituting a heart healthy lifestyle should also be prescribed a medication to lower their BP while they continue to work on weight loss and lifestyle changes (11).

As with any medication, the particular agent chosen should be aimed at treating the underlying etiology, with particular attention being paid to comorbid conditions. As activation of the RAAS system is one of the main ways in which obesity contributes to elevated BP and hypertension, it follows that angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) would be appropriate initial agents in the treatment of obesity-related hypertension. In addition to being able to directly target pathways leading to elevated BP, ACEi or ARB may also have beneficial effects on diabetes and dyslipidemia, two common comorbidities in overweight and obese individuals (46).

Some agents are less ideal in the treatment of obesity-related hypertension. Diuretics, for example, may have similar antihypertensive efficacy as ACEi/ARB in hypertensive, obese adults and may be associated with lower CV events in adults, but they also reduce intravascular volume and cardiac output and stimulate the SNS and RAAS. These agents can also worsen insulin resistance and dyslipidemia and can increase glucose and uric acid levels, particularly in obese individuals. Beta-blockers reduce BP by decreasing both cardiac output and renin activity. However, these agents can lead to weight gain and increased triglycerides and decreased HDL-cholesterol levels. They also have inferior outcomes in adults, particularly when restricted to obese subjects, which may be related to these known side effects (47, 48).

As with non-obesity-related hypertension, the goal of therapy is to lower BP. BP should be treated to below the 90th percentile, or below 130/80 for children $\geq$ 13 years old (18).

## CONCLUSION

Obesity-related hypertension is highly prevalent among US children. There are multiple mechanisms by which obesity can lead to elevated BP and increased CVD risk. Central to this is adipose tissue dysfunction, related to an imbalance in the pro- and anti-inflammatory activities of the adipocyte. First-line antihypertensive therapy for children with obesity-related hypertension is weight loss. In addition, instituting a heart healthy lifestyle that includes daily physical activity and a diet rich in fruits and vegetables, fiber and low-fat dairy, that is also low in carbohydrates and sugar-sweetened beverages is essential in the treatment of obesity-related hypertension. There may be challenges to this in children with obesity, related to comorbid conditions such as depression, anxiety, and decreased mobility. A multidisciplinary approach is often required for maximal effectiveness. Some children will require antihypertensive pharmacologic therapy. In children, no agent has been shown to be more effective at lowering BP than another. However, the decreased CV events found among adults treated with RAAS blockers and the adverse metabolic profile associated with beta blocker and diuretic use, make RAAS blockade potentially beneficial in the treatment of pediatric obesity-related hypertension.

## AUTHOR CONTRIBUTIONS

TB was the sole contributor to the structure of the work and to the acquisition and interpretation of data for the work. TB was solely responsible for drafting the work, provided final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REVIEW
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# Hypertension in the Pediatric Kidney Transplant Recipient

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Hypertension after kidney transplant is a frequent occurrence in pediatric patients. It is a risk factor for graft loss and contributes to the significant burden of cardiovascular disease (CVD) in this population. The etiology of posttransplant hypertension is multifactorial including donor factors, recipient factors, medications, and lifestyle factors similar to those prevalent in the general population. Ambulatory blood pressure monitoring has emerged as the most reliable method for measuring hypertension in pediatric transplant recipients, and many consider it to be essential in the care of these patients. Recent technological advances including measurement of carotid intima-media thickness, pulse wave velocity, and myocardial strain using specked echocardiography and cardiac magnetic resonance imaging have improved our ability to assess CVD burden. Since hypertension remains underrecognized and inadequately treated, an early diagnosis and an appropriate control should be the focus of therapy to help improve patient and graft survival.

**Keywords: kidney transplant, hypertension, pediatric, ambulatory blood pressure monitoring, carotid intima–media thickness, pulse wave velocity, antihypertensive drugs**

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## INTRODUCTION

Hypertension after renal transplantation is a common phenomenon with an estimated prevalence of 70–90% in adults and 58–89% in children (1–3). Long-standing hypertension has been associated with allograft dysfunction, premature atherosclerosis, and cardiomyopathy (4, 5).

Cardiovascular disease (CVD) is much more common among children with chronic kidney disease (CKD) and end-stage renal disease (ESRD) compared to the general population. CVD accounts for a large proportion of morbidity and mortality in this population (6). Renal transplantation improves CVD risk. Compared to patients awaiting transplantation, transplant recipients experience a substantial reduction in the CVD-associated death rate, especially from adolescence onward while they maintain good graft function (7–11). However, hypertension remains a significant and modifiable risk factor for CVD in pediatric transplant recipients. Studies have shown that transplant patients have better systolic and diastolic function than those receiving hemodialysis or peritoneal dialysis (PD), despite having increased prevalence of hypertension and left ventricular hypertrophy (LVH) (12). In addition to offering transplantation to ameliorate the cardiovascular effects of ESRD, aggressively treating blood pressure in transplant recipients would further reduce the prevalence of CVD.

The etiology of posttransplant hypertension is multifactorial encompassing donor-associated factors, side effects of immunosuppressive medications, underlying recipient disease, and possibly genetic factors, as seen in **Figure 1**. The treatment strategies vary by timing after transplant as well as the pathophysiological contributors to hypertension. This review will cover etiology of posttransplant hypertension, effects of hypertension on the patient, graft survival, assessment methods, and treatment options.

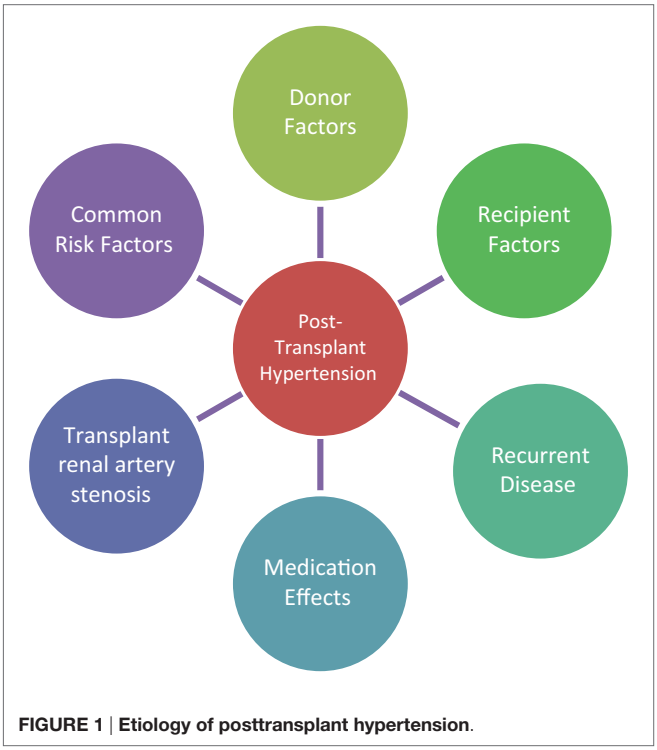


**FIGURE 1 | Etiology of posttransplant hypertension.**

# ETIOLOGY OF HYPERTENSION

## Donor Factors

It has been well established that several independent donor risk factors predispose the transplant recipient to hypertension including deceased donor, older age, and donor hypertension (13, 14). It is theorized that the increased risk comes from longer cold ischemia time, damaged graft vessels from hypertension, and age-related glomerular dropout in older donors. Due to these reasons, most transplant centers do not accept donors beyond a certain age or those with hypertension for pediatric recipients except in extenuating circumstances. Extended criteria donor kidneys have been associated with increased risk of death from CVD in the adult population and usually are not accepted for pediatric recipients (15).

The kidney donor profile index (KDPI) scoring system, used to evaluate donor grafts, was recently introduced in the United States (16). Donors with lower KDPI have potential for better graft survival, and pediatric recipients get preference for donors with lower KDPI scores, and most pediatric transplant centers will not accept kidneys with high KDPI scores for children. There are no data yet on long-term CVD outcomes for transplant recipients based on donor KDPI scores.

Recently, donor genetic variants have been found to contribute to poor graft function and posttransplant hypertension. Polymorphisms including apolipoprotein L1 (*APOL1*), ATP-Binding Cassette Subfamily B Member 1 (*ABCB1*), Caveolin 1 (*CAV1*), and ATP-Binding Cassette Subfamily C Member 2 (*ABCC2*) have been shown to affect graft survival, hypertension, and calcineurin-induced nephrotoxicity (17–21). Currently, there is no standard for screening for these polymorphisms.

## Recipient Factors

Recipient factors such as recurrence of original disease in the graft and presence of native kidneys are known contributors to posttransplant hypertension. Occasionally, native nephrectomies are performed prior to or at the time of transplant to help with management of hypertension (22). However, this is becoming an uncommon practice because recent data suggest that the benefit is limited (23).

Pediatric patients with pretransplant obesity have significantly higher systolic blood pressure (SBP) and worse glomerular filtration rate (GFR) than children with normal body mass index prior to transplant (24). The incidence of pretransplant obesity is increasing mirroring the rise of obesity in the general pediatric population (25). As in the general population, the development of overweight or obesity after transplantation in children is associated with hypertension and poor glycemic control (26, 27). While these CVD risk factors can more pronounced due to the known side effects of immunosuppressant medications, the effect of obesity on hypertension in the pediatric transplant recipient has been shown to be independent of posttransplant use of steroids (28).

## Effects of Medications

Immunosuppressive medications play a significant role in the development of posttransplant hypertension. It has been well established that corticosteroids induce hypertension by increasing renal salt and water reabsorption and increase in renal vascular resistance. Studies have shown that patients on steroid-minimization protocols and patients undergoing late-withdrawal of steroids showed reduction in hypertension and obesity and improved lipid and carbohydrate metabolism (29).

The incidence of posttransplant hypertension significantly increased after calcineurin inhibitors (CNI) such as cyclosporine and tacrolimus became commercially available for use. A recent Greek cohort of pediatric transplant patients showed that there was an increased risk of hypertension for patients on a CNI-based immunosuppression protocol (14).

The mechanism of CNI-induced hypertension is primarily mediated by glomerular afferent arteriolar constriction leading to increased salt and water retention, in part through upregulation of the thiazide-sensitive Na+-Cl− cotransporter (30, 31). Additional mechanisms include activation of renin angiotensin aldosterone system and secretion of reactive oxygen species (32, 33). An imbalance between vasoconstrictive molecules (endothelin, thromboxane, and prostaglandins) and vasodilatory nitric oxide also contributes to the development of hypertension (34, 35). Finally, prolonged CNI exposure causes increased production of transforming growth factor-β production, which leads to fibrosis and long-term graft damage (36–38). Tacrolimus has become the preferred CNI in clinical practice as it causes less hypertension and hyperlipidemia, as well as improved graft survival when compared to cyclosporine (39, 40).

Previously, it has been shown that mammalian target of rapamycin (mTOR) inhibitors act synergistically with CNI to worsen hypertention (41). Brunkhorst et al. (2015) recently compared the efficacy and safety of an everolimus and low-dose CSA regimen to standard dose cyclosporine and mycophenolate mofetil

therapy in 105 pediatric transplant patients. They found that the everolimus group had comparable graft function and survival but more dyslipidemia and arterial hypertension than the control group (42). This suggests that mTOR inhibitors have an effect on posttransplant hypertension independent of or in synergy with the CNI effect, although the precise mechanism is not yet known.

## Transplant Renal Artery Stenosis (TRAS)

Transplant renal artery stenosis is the most common vascular complication after renal transplant, usually presenting 2 months–2 years after transplant (43). Clinical signs are usually worsening or refractory hypertension with or without graft dysfunction (44). It has a reported prevalence of 1–23% and accounts for 1–5% of posttransplant hypertension (45).

Risk factors for TRAS include surgical technique, deceased donor, cytomegalovirus infection, and prolonged ischemia time (46). A recent study investigated the role of genetic polymorphisms in the myosin heavy chain 9 (*MYH9*) gene on TRAS. The product of this gene is heavily expressed in glomeruli, tubular, and renal capillaries as well as arteriolar endothelial cells. Donor organs found to carry the rs3752462 CC variant had a 10.9-fold increase in TRAS compared to the recipients carrying rs5756168 TT variant that had a 3.45-fold decrease in risk (47).

## Graft Dysfunction

### Recurrent and *De Novo* Glomerular Diseases

Many underlying glomerular diseases in the recipient can recur in the transplant allograft including focal segmental glomerulosclerosis (FSGS), atypical hemolytic uremic syndrome (aHUS), antiglomerular basement membrane disease, systemic lupus erythematosus nephritis, membranous glomerulonephritis (MGN), and membranoproliferative glomerulonephritis. Of these, the most common are aHUS and FSGS, the latter with a 30–50% recurrence risk in the first transplant and 80–100% in subsequent transplants (48). Some transplant patients develop *de novo* glomerular disorders after transplant that may include FSGS and MGN. These glomerular disorders have the potential to cause hypertension, and poor blood pressure control will accelerate renal function decline (49–51).

### Acute Rejection (AR)

Acute rejection can be T-cell and antibody mediated and is often associated with hypertension. Any transplant patient with sudden onset or worsening of hypertension should be assessed for AR. The hypertension in this case usually responds well to treatment of AR.

### Chronic Rejection, Also Known As Chronic Transplant Glomerulopathy (TG)

Transplant glomerulopathy causes hypertension through progressive scarring and fibrosis. Recent data showed that non-HLA autoantibodies targeting the angiotensin II type-1 receptor have been linked to hypertension, and treatment with an angiotensin receptor blocker may be beneficial (52–54).

## Common Risk Factors Prevalent in the General Population

While patients with ESRD have numerous additional risk factors compared to normal children for developing hypertension, common risk factors for hypertension present in the general population also prevail in kidney transplant recipients. These risk factors include tobacco smoking, illicit drug use, medications for attention deficit hyperactivity disorder, high-salt diet, physical inactivity, obesity, sleep disturbances including obstructive sleep apnea, and genetic determinants of hypertension (55–59). **Figure 2** outlines the common etiologies

| 0 – 1 week | 1 – 2 Months | 2 – 12 Months | 1 – 10 Years |
|---|---|---|---|
| **Fluid overload** | **High-dose CNI** | **Medication effects** | **Acute rejection** |
| **High dose steroids** | **Recurrent disease** | **Acute rejection** | **Chronic transplant glomerulopathy** |
| **Delayed graft function** | **Underlying native kidney disease** | **Recurrent disease** | **Renal artery stenosis** |
| **Underlying native kidney disease** | | **Renal artery stenosis** | **Medication effect** |
| **Recurrent disease** | | **Obesity** | **Recurrent disease** |
| | | **Lifestyle** | **De novo glomerulonephritis** |
| | | | **Obesity** |
| | | | **Lifestyle** |
| | | | **Nocturnal sleep apnea** |
| | | | **Genetic determinants** |

**FIGURE 2** | **Etiology of hypertension by time after transplant**.

observed for post-transplant hypertension in relation to time after transplant.

## EFFECT OF HYPERTENSION ON CVD AND ALLOGRAFT FUNCTION

Definitive cardiovascular outcomes such as stroke, myocardial infarction, and death are uncommon in the pediatric age group. Pediatric studies have relied on the use of intermediate endpoints such as LVH as measured by left ventricular mass index (LVMI), carotid intima-media thickness (cIMT), and pulse wave velocity (PWV) for CVD risk stratification. It has been well described that pediatric patients with CKD and ESRD have significantly increased cardiovascular morbidity and mortality compared to their healthy peers (60, 61). CVD accounts for approximately 30% of mortality among pediatric kidney transplant recipients (9).

Long-standing hypertension has been shown to result in LVH and increased LVMI and cIMT, all known risk factors for CVD (2). LVH is prevalent in approximately 50% of patients with CKD and ESRD and in kidney transplant recipients. A single-center study comparing pretransplant echocardiography (ECHO) with posttransplant ECHO showed that interval decrease in indexed SBP was the only predictor of LVMI improvement on multivariate analysis (62). A cross-sectional study in 2004 found that children with a kidney transplant were more likely to have elevated LVMI and diastolic dysfunction than healthy controls (63). However, another study found no difference in systolic or diastolic function between normotensive and hypertensive pediatric transplant recipients using the same tissue Doppler technique (2).

Evidence suggests that hypertension itself, regardless of BP level, is associated with LVH. Specifically, Hamdani et al. showed that treated hypertensive individuals with a normal blood pressure had a greater prevalence of LVH than normotensive individuals not treated with antihypertensive medications. In this same study, a large pediatric cohort of 221 patients evaluated with ambulatory blood pressure monitoring (ABPM), it was noted that patients with normal blood pressure who did not require antihypertensive medications had less allograft dysfunction than patients taking antihypertensive medications and even in those whose BP was in normal range (64). This emphasizes the point that children with pharmacologically controlled hypertension are still at an increased CVD risk compared to normotensive individuals and require close screening for intermediate risk factors and endpoints.

Masked hypertension as determined by ABPM in both patients receiving and not receiving antihypertensive therapy has an estimated prevalence of 25–35% (65). While smaller studies have not been able to find an association between masked hypertension and graft function, a recent study by Hamdani et al. showed that pediatric transplant recipients with masked hypertension had significantly worse graft function than their normotensive peers (66).

A study aimed at assessing CVD risk factors in pediatric transplant patients found that there was a negative correlation between GFR and SBP ± diastolic blood pressure (DBP) on univariate analysis. There was a noted trend of worsening hypertension with increasingly poor graft function on multivariate analysis, but the study was underpowered to detect this effect (67). A Finnish cohort found that only decreased diastolic dipping could predict lower GFR (68). More recently in a Greek cohort, 20-year graft survival was superior for patients without hypertension at 10 years follow-up after kidney transplant compared to those with hypertension (100 vs. 44.4%, $P < 0.05$) (14). As well established in native kidneys with CKD, the presence of poorly controlled hypertension also negatively affects renal graft function over time.

A Dutch cohort study looking at long-term CVD outcomes in kidney transplant recipients (with an average follow-up of 15. 5 years) who developed ESRD as children (0–14 years of age) found that ~50% of males and 40% of females had LVH, 13% had diastolic dysfunction, and aortic valve calcification was seen in 25% males and 12% female patients (69). Duration of PD was independently associated with development of aortic valve calcifications and diastolic dysfunction increased over time and correlated with low GFR. This study also demonstrated an era effect as patients who developed ESRD in the 1970s and 1980s had increased prevalence of CVD prior to more aggressive blood pressure control, ubiquitous use of erythropoietin-stimulating agents, frequent avoidance of aluminum, and limited use of calcium-based phosphorus binders (69). A similar recent Dutch cohort still continued to show era effects in CVD outcomes with improved management of hypertension and hyperlipidemia (70).

In conclusion, children with CKD/ESRD come to transplant with significant burden of hypertension and CVD. With transplantation, their CVD risk improves overall but may be negatively impacted by poor control of blood pressure, by decline in GFR overtime, and by the presence of hyperlipidemia, obesity, and hyperglycemia.

## BLOOD PRESSURE MEASUREMENT AND ASSESSMENT OF CVD RISK

Screening for hypertension can be achieved by several methods that include casual clinic blood pressure measurement, home and school blood pressure measurement, and 24-h ABPM. ABPM has been shown to be the most reliable method for measuring blood pressure. It also has the added benefit of determining BP load and predicting LVH (71–73). Pediatric patients with ESRD who lack nocturnal dipping as characterized by a decrease of >10% in nighttime blood pressure compared to daytime blood pressure are deemed to be at an increased risk of LVH. However, this was not borne out in another recent study that showed that hypertensive children without ESRD who have nocturnal non-dipping have similar prevalence of LVH compared to hypertensive children without non-dipping (74, 75).

Before widespread use of ABPM, we must recognize its current limitations. Primarily, controversy remains about how to best interpret ABPM results due to lack of diverse normative data. Currently available normative data are based on ABPM measurements of 949 healthy children published by the German Working

Group of Pediatric Hypertension (76). All children included in this study were of European descent, relatively few short children (<140 cm) were included, and there was a lack of variability in DBPs within the group raising question about the algorithm used to calculate the normal values.

## Carotid Intimal Media Thickness

High-resolution ultrasonography provides a non-invasive method for measuring cIMT. Increased cIMT, a marker for the development and progression of vascular calcification, has been documented in children as young as 8 years and correlates with duration of CKD, time on dialysis, hyperhomocysteinemia, and increased calcium–phosphorus product (77, 78). A recent meta-analysis showed that pediatric solid organ transplant recipients have increased cIMT compared to healthy controls (79). Increased cIMT has been shown to be a strong risk factor for myocardial infarction and stroke in adults (80). Childhood hypertension has been shown to predict increased adult cIMT by the Childhood Cardiovascular Cohort (i3C) (81).

Hypertension has been shown to have a linear correlation with cIMT in adults (82). Balzano et al. showed that although renal transplant recipients had increased cIMT and LVMI compared to healthy controls, there was no progression or worsening in those who underwent annual ABPM monitoring and had well-controlled hypertension (83). This study is reassuring of the fact that while renal transplant recipients have greater cIMT and LVH than healthy controls, regular blood pressure monitoring and aggressive blood pressure control can halt the progression of these intermediate CVD outcomes.

## Pulse Wave Velocity

Arterial PWV is a sensitive marker of arterial stiffness, which makes it a good surrogate endpoint for CVD (84). Increased arterial stiffness is an independent predictor of survival in the general population and in CKD patients (85). Normative pediatric reference values are available based on a study of 1,000 healthy children, which enabled the calculation of age- and height-specific SD scores (86). This study was performed on patients in Hungary, Italy, and Algeria with ages ranging between 6 and 20 years. Multiple regression analysis showed that age, height, and blood pressure were major predictors of PWV.

Chronic kidney disease patients have been shown to have increased PWV. The recent 4C Study looked at numerous cardiovascular endpoints including PWV and found that 20.1% of CKD patients in their cohort had elevated PWV. In their analysis, the rise in PWV was independent of eGFR and moderately correlated with cIMT (87). Sinha et al. (2015) showed that in children with advanced CKD, only poorly controlled hypertension but not GFR was associated with a change in arterial stiffness when compared to healthy matched controls (88). In addition, the Young Finn study showed that childhood hypertension was related to higher adult PWV (89). In pediatric kidney transplant recipients, PWV has been shown to be increased compared to control patients matched for age and weight/height (26, 90). Since pediatric kidney transplant recipients have ongoing CKD, strict BP control may help to lower PWV and future cardiovascular risk in this population.

## Myocardial Strain Analysis

The majority of coronary artery disease in CKD patients is asymptomatic and may initially present with arrhythmia and sudden death. Assessing the degree of myocardial strain using ECHO or magnetic resonance (MR) imaging can detect more subtle changes of impaired cardiovascular function, thus offering an opportunity for early intervention.

Echocardiographic strain imaging helps to objectively quantify myocardial function (91). An extension of this is global longitudinal strain (GLS) analysis, which can be used to detect subtle changes in left ventricular function. GLS has been shown to be independently associated with all-cause and CV mortality in adult patients with CKD and after renal transplant. It is a more reliable marker than ejection fraction for mortality (92, 93). Pirat et al. demonstrated that ESRD patients with a normal ejection fraction had signs of subclinical myocardial disease as determined by impaired longitudinal, circumferential, and radial strain as well as strain rate (94). In that same study, patients who underwent renal transplantation had improvement in all of these parameters compared to the patients receiving chronic dialysis. The clinical characteristics that negatively affect GLS and basal longitudinal systolic strain were shown to include increased interventricular septal thickness, diabetes, low ejection fraction, increased DBP, and regular dialysis (95). This again highlights the role of hypertension as a modifiable risk factor.

Cardiac MR is a relatively newer imaging modality that can provide additional information about CV risks in the CKD population. Blood oxygen level-dependent cardiac MR can be used to assess myocardial tissue oxygenation. A recent study employing this technique found that patients with CKD and renal transplant without known coronary artery disease had impaired myocardial response to stress, independent of the presence of diabetes mellitus, LVH, and myocardial scar (96). An additional use for cardiac MR imaging is to estimate LVM, which has been shown to closely correlate with autopsy findings of heart size. A recent study compared ECHO and cardiac MR in their ability to measure LVM in hypertensive pediatric patients and found that ECHO generally overestimated the presence of LVM and cardiac MR was a much more reliable method (97).

As these technologies become more readily available and cost-effective in clinical practice, they will be able to offer more reliable tools to assess cardiovascular dysfunction in pediatric transplant recipients.

# MANAGEMENT OF HYPERTENSION

## Acute Postoperative Management

There are no published guidelines or recommendations for the immediate postoperative management of kidney transplant recipients. We will describe our center's practice based on our clinical experience in this section. In the immediate postoperative period (first week), the most likely etiology of hypertension is fluid overload, side effect of high-dose steroid therapy for induction, and native kidney disease. In the first few postoperative days, permissive hypertension is tolerated to ensure adequate

graft perfusion especially in small children. Size discrepancy of the donor and recipient arteries and relatively lower blood pressure in the child can compromise early graft perfusion and predisposition to thrombus formation. This necessitates higher patient blood pressures and may require vasopressor support to achieve this.

After a few days postoperatively, excess fluid begins to mobilize and move into the intravascular space, contributing to hypertension. Allowing gradual diuresis back to the patient's dry weight will often result in decrease of the systemic blood pressure. However, patients frequently need to be restarted or initiated on antihypertensive medications during the postoperative period.

## Long-term Management

A holistic approach to the long-term management of hypertension should be pursued in the pediatric transplant recipient. As the goal of hypertensive management is ultimately to prolong patient and graft survival and decrease CVD, this approach should include close monitoring and management of graft function as well as adherence to medications, diet, and exercise. Many review papers have been published on the pharmacologic management of hypertension (1, 98, 99). The current KDIGO position is that no class of antihypertensive medications is contraindicated in transplant recipients (100). In clinical practice, calcium channel blockers (CCBs) and ACE-I are the most common first-line medications (101–103). While permissive hypertension is tolerated immediately after transplant surgery, the ultimate goal of therapy should be to target normal blood pressures (<90th percentile) and try to achieve control near the 50th percentile for age.

As with hypertension in patients without renal transplant, pharmacologic therapy should be aimed at addressing the underlying etiology. In patients on CNI-based immunosuppression, afferent arteriole vasoconstriction contributes to hypertension, and therefore, a use of CCBs is usually the first-line therapy due to its vasodilatory properties. CCBs have a very good safety profile and have been shown to be efficacious in this patient population for both blood pressure control and improvement of GFR compared to placebo treated patients (101). In non-transplant patients, the benefit of ACE-I in the pediatric CKD population with proteinuria has been well described (51). Less concrete evidence exists for the use of ACE-I in kidney transplant recipients. Knoll et al. performed a multicenter double-blind placebo-controlled study comparing ramipril to placebo and found no benefit in allograft survival in the treatment group. His study was underpowered to detect a difference and may account for their null results (104). A recent meta-analysis to look at the effects of ACE-I on graft survival also found no benefit (105). A small case series in a pediatric population found that ACE-I appeared to stabilize creatinine in patients with chronic allograft dysfunction, but statistical analysis could not support the renoprotective effect of ACE-I on long-term graft survival (106). Meta-analysis by Cross et al. showed that therapy with ACE-I can reduce proteinuria, however there are not enough data to support that this improves graft survival (101). Diuretics are not usually employed in the pediatric transplant population due to the need to maintain adequate hydration; however, a thiazide diuretic may be effective in helping control CNI-mediated hypertension due to its action through the thiazide-sensitive Na-Cl channel (30, 107).

## Dietary Counseling

While pharmacological interventions have an important role in the management of hypertension, dietary and exercise counseling need to be at the forefront of long-term management of transplant recipients.

Diets high in sodium and low in potassium have been shown to aggravate hypertension. In a Belgian study of adult patients, dietary history and urinary sodium and potassium excretion were evaluated. While sodium intake did not differ between the two groups (~10 g/day), patients with controlled blood pressure consumed higher amounts of potassium by regularly eating more fruits and vegetables, which lowered their observed Na+/K+ ratio (108). Asai et al. demonstrated that repeated dietary counseling resulted in a statistically significant reduction in mean 24-h urinary sodium excretion and SBP (109). Similarly, de Vries et al. also showed that dietary sodium restriction in adult kidney transplant recipients resulted in statistically significant reductions in SBP and DBP (110). Both of these studies had small sample size, and therefore, it is impressive that the noted changes in blood pressure were able to reach statistical significance.

In accordance with these findings, published nutritional guidelines for renal transplant recipients include low-sodium diet and weight loss in obese individuals to optimize blood pressure management (111). Counseling of patients should be done routinely, as infrequent counseling has been shown to be not effective (112).

## Systems-Based Approach

Changes and improvement in management of hypertension in the pediatric kidney transplant population can be approached using quality improvement methodology. Because this is a complex multifaceted problem that affects patients' long-term outcomes and requires multidisciplinary cooperation, this can be addressed by employing the Chronic Care Model as suggested by Hooper and Mitsnefes (113). Recommendations include implementation of clinic visit checklists to ensure that blood pressure, diet, and lifestyle risk factors are addressed regularly at every clinic visit, augmenting the electronic health record (EHR) to calculate blood pressure percentiles, pop-up reminders for annual ABPM screening, and employing novel technology to encourage activity and participation among transplant recipients.

# CONCLUSION

Hypertension in the pediatric kidney transplant recipients is highly prevalent and often underrecognized and undertreated. This contributes to worse allograft function and long-term risk of CVD in early adulthood and partly accounts for the significantly increased mortality in this patient population. Hypertension is a modifiable risk factor that should be aggressively monitored and treated, as summarized in **Figure 3**. Annual 24-h ABPM and

**Key Points**

- **Prevalence is very high**
- **Multifactorial etiology**
- **Frequently under recognized and undertreated**
- **Significant contributor to long-term morbidity and mortality**
- **Controlled hypertension helps to preserve allograft function and decrease cardiovascular morbidity and mortality**

**FIGURE 3** | **Key points**.

echocardiography are useful tools to asses CVD risk and monitor blood pressure control. Newer technologies such as measurement of cIMT, PWV, and myocardial strain can be considered to enhance CVD risk stratification. Treatment should include a combination of pharmacological and lifestyle interventions to optimize care utilizing a multidisciplinary team. Currently, quality improvement methodology and EHR technology provide an opportunity to customize workflows and build in templates/reminders to optimize patient care and improve patient outcomes.

## FUTURE RESEARCH

There are many gaps in our knowledge in this field that would benefit from further research including but not limited to CVD outcomes based on the donor KDPI; genetic polymorphism of donors affecting posttransplant hypertension in transplant recipients; ABPM normative data of diverse ethnic populations; blood pressure percentile treatment goals for transplant recipients; effect of ACE-I on long-term graft survival, and finally, addressing barriers to adherence at both provider and patient level with adequate treatment plan.

## AUTHOR CONTRIBUTIONS

OC wrote the manuscript under guidance and supervision by AM. Both parties were directly involved and were the only contributors to the production of the manuscript.

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REVIEW
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# Review of Pediatric Pheochromocytoma and Paraganglioma

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Pheochromocytoma (PCC) and paraganglioma (PGL) are rare chromaffin cell tumors which secrete catecholamines and form part of the family of neuroendocrine tumors. Although a rare cause of secondary hypertension in pediatrics, the presentation of hypertension in these patients is characteristic, and treatment is definitive. The gold standard for diagnosis is *via* measurement of plasma free metanephrines, with imaging studies performed for localization, identification of metastatic lesions and for surgical resection. Preoperative therapy with alpha-blocking agents, beta blockers, and potentially tyrosine hydroxylase inhibitors aid in a safe pre-, intra- and postoperative course. PCC and PGL are inherited in as much as 80% of pediatric cases, and all patients with mutations should be followed closely given the risk of recurrence and malignancy. While the presentation of chromaffin cell tumors has been well described with multiple endocrine neoplasia, NF1, and Von Hippel–Lindau syndromes, the identification of new gene mutations leading to chromaffin cell tumors at a young age is changing the landscape of how clinicians approach such cases. The paraganglioma–pheochromocytoma syndromes (SDHx) comprise familial gene mutations, of which the SDHB gene mutation carries a high rate of malignancy. Since the inheritance rate of such tumors is higher than previously described, genetic screening is recommended in all patients, and lifelong follow-up for recurrent tumors is a must. A multidisciplinary team approach allows for optimal health-care delivery in such children. This review serves to provide an overview of pediatric PCC and PGL, including updates on the preferred methods of imaging, guidelines on gene testing as well as management of hypertension in such patients.

**Keywords: pheochromocytoma, paraganglioma, pediatrics, SDHx hereditary paraganglioma–pheochromocytoma syndromes, phenoxybenzamine, metyrosine, long-term follow-up**

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## INTRODUCTION

The rare neuroendocrine tumors pheochromocytoma (PCC) and paraganglioma (PGL) are the cause of hypertension in 0.5–2% of pediatric cases (1, 2). PCCs arise from the adrenal medulla and comprise 80–85% of catecholamine-secreting tumors while PGLs arise from extra-adrenal locations and are subdivided into sympathetic and parasympathetic PGLs, accounting for 15–20% of these tumors (3). Sympathetic PGLs arise along the sympathetic ganglion chain (4) in the chest, abdomen, and pelvis. Parasympathetic PGLs arise from parasympathetic tissue in the head and neck (HNPGL); these rarely secrete catecholamines. PCCs and PGLs have different

catecholamine-secreting profiles. Tyrosine is the precursor to catecholamines, which through a series of enzymatic reactions is converted to DOPA by the enzyme tyrosine hydroxylase. DOPA is converted to dopamine, which is further converted to norepinephrine and finally changed to epinephrine. The distinction between the types of hormones secreted by adrenal or extra-adrenal tumors comes from the enzyme phenylethanolamine *N*-methyltransferase (PNMT) present in the adrenal gland, with its expression dependent upon onsite cortisol. PNMT can convert norepinephrine to epinephrine (5) and as such, tumors secreting epinephrine and frequently norepinephrine are generally from the adrenal gland while extra-adrenal tumors secrete norepinephrine and dopamine. PCCs and PGLs occur sporadically as well as in the context of hereditary syndromes to include multiple endocrine neoplasia (MEN) type 2, Von Hippel–Lindau (VHL) type 2, neurofibromatosis (NF) type 1, and the paraganglioma–pheochromocytoma syndromes (SDHx). The reported inheritance has changed from 30 to 40% in small pediatric case series (1, 6–10) to 80% in a larger series (11) and other susceptibility genes, not currently ascribed to syndromes, have been identified.

## CAUSES OF HYPERTENSION IN PEDIATRICS

The overall prevalence of hypertension has risen from 2 to 4.5% (12, 13) in the pediatric population, with much of this increase attributed to obesity induced hypertension. Secondary hypertension is more common in younger children resulting from reno-vascular or renal parenchymal disease (78–80% of causes) (14, 15), endocrine (11% of causes) (14), cardiac (2% of causes) (16), pulmonary and others as shown in **Table 1**. Since PCCs and PGLs account for only 0.5–2% (2) of secondary hypertension, one should be mindful to rule out more common causes when evaluating a child with elevated blood pressure (BP). As depicted in **Table 1**, taking into account symptomatology, as well as laboratory findings and a family history may point toward a catecholamine-secreting tumor.

## CLINICAL PRESENTATION

The average age at presentation of PCCs and PGLs in pediatrics is 11–13 years, with a male preponderance of 2:1 (11, 17, 18). The clinical presentation is variable, with sustained hypertension seen in 60–90% of pediatric cases (17–19). In contrast, adults exhibit paroxysmal hypertension in about 50% of cases. One case series described 67% of children with headaches in addition to hypertension (17), while palpitations, sweating, pallor, nausea, and flushing were seen in 47–57% of children (1, 3, 4, 17, 19, 20). Anxiety, weight loss, and visual disturbance (7) were manifested in some while polyuria and polydipsia were reported as the only presenting symptoms in one case study (21). Symptomatology may depend on the type of hormone being secreted. Individuals with epinephrine secreting tumors can present with hypoglycemia and hypotensive shock, from excess catecholamine production and circulatory collapse. Dopamine-secreting tumors are usually asymptomatic, delaying diagnosis until the mass effect of the tumor is apparent (22). The mass effect from non-functional head and neck paragangliomas (HNPGLs) can lead to dysphagia, hoarseness, hearing disturbances, and pain.

## GENETICS OF PCC AND PGL

Contrary to historic belief of the "rule of 10" for PCCs and PGLs that 10% are hereditary, 10% are malignant, 10% are extra-adrenal, and 10% are bilateral, their inheritance is much higher in reported pediatric case series. The European-American-Pheochromocytoma-Paraganglioma-Registry (EAPPR) followed 164 unrelated pediatric patients diagnosed with PCCs/PGLs, 80% of which had a germline mutation in a gene associated with such tumors (11). Previous to this registry, the estimated percentage of germline mutations was 30–40% in smaller pediatric case series (1, 4, 7–10, 23). This change in prevalence is multifactorial and may result from increased screenings for mutations, novel identification of mutations as well as data from the EAPPR being more reflective of a population-based frequency.

In addition to the known syndromic presentations of MEN II, NF1, and VHL, germline succinate dehydrogenase gene mutations (SDHx) involving the mitochondrial enzyme complex (SDH) form part of the familial PGL–PCC syndromes. SDH consists of the four subunits SDHA, SDHB, SDHC, and SDHD; SDHAF2 is one of the factors involved in the assembly of the SDH complex. These syndromes are inherited in an autosomal dominant fashion with varying penetrance. The Carney triad syndrome (described in 1977), Carney–Stratakis syndrome (described in 2002) and Pacak–Zhuang syndrome (described in 2013) are rare syndromes with PGLs as one of the presenting features.

The Carney triad syndrome constitutes gastrointestinal stromal tumors (GISTs), PGLs, and pulmonary chondromas. There is no known genetic defect identified to date. Sporadic GISTs are distinct from those associated with Carney triad in the staining pattern they exhibit. In pediatrics, GISTs are found in the stomach with negative SDHB staining, which is defined as a loss of a granular cytoplasmic pattern in the presence of valid positive controls (24). In adults, GIST is primarily found along the GI tract excluding the stomach, and these tumors are SDHB positive. When adult patients have GIST originating from the stomach, the histology and staining of these tumors resemble pediatric GIST (24). The mean age of presentation is 21 years with young women being predominantly affected. In one study of 79 patients, 47% presented with PGLs or PCCs, the majority of which (37 patients) were PGLs (92%) (25, 26).

The Carney–Stratakis syndrome has an autosomal dominant pattern of inheritance and is a diad that comprises of GISTs and PGLs. Most patients have been found to carry germline mutations in SDHB, SDHC or SDHD. It is rare and was identified in about 20 kindreds (27); 58% of 12 patients with this syndrome only had PCC/PGLs with the youngest child reported in the literature being 12 years old (28).

The Pacak–Zhuang syndrome has the gene mutation in hypoxia-inducible factor 2 alpha with clinical features of HNPGLs, somatostatinomas, and polycythemia (29). In a series of seven patients, of which three were pediatric cases with PCCs and/or

**TABLE 1** | Secondary causes of hypertension by organ system with clinical and laboratory findings.

| Organ system | Differential diagnosis | Findings/workup |
|---|---|---|
| **Renal** | | |
| Renal parenchyma | Acute and chronic glomerulonephritis | Hematuria, proteinuria, edema |
| | Acute and chronic renal failure | Use KDIGO, pRIFLE, or AKIN guidelines for diagnosis |
| | Congenital renal malformations[a] | Prenatal/postnatal renal US findings of dysplasia, obstructive uropathy |
| | Polycystic kidney disease | Hepatosplenomegaly (ARPKD) |
| | Systemic vasculitis | |
| | SLE | Low C3, C4, CH50, +ds-DNA, +anti-Smith, joint pain/swelling, rash, edema |
| | ANCA | Normal to +ANCA, ↑ CRP, ↑ ESR, joint pain/swelling, rash, edema |
| | HSP | Hematuria, proteinuria, purpuric rash |
| | PAN | Arteriography, ↑ liver enzymes, livedo reticularis |
| | Parenchymal scar from pyelonephritis, VUR, HUS | DMSA scan; VCUG and history of UTIs; hemolysis, uremia, +/– diarrhea, AKI |
| Reno-vascular | Renal vein thrombosis[a] | Hematuria, thrombocytopenia, flank mass |
| | Renal artery stenosis | Abdominal bruit, angiogram, and renal vein sampling |
| | Fibromuscular dysplasia | |
| | Syndromes | |
| | Williams | Elfin facies, short stature, hypercalcemia, supravalvular aortic stenosis, "cocktail party" personality, CAKUT |
| | Turners | Webbed neck, widely spaced nipples, short stature, ovarian failure, cardiac malformation, CAKUT |
| | NF1 | Neurofibromas, café-au-lait spots, axillary freckling, Lisch nodules, optic gliomas, bone and CNS abnormalities |
| | Arteritis | |
| | Takayasu's | Bruit, angiogram |
| | Kawasaki | Conjunctival injection, strawberry tongue, erythema of the extremities, cervical lymphadenopathy, polymorphous rash, ↑ WBCs and platelets, ↑ liver enzymes, ↑ ESR, ↑ CRP |
| | Moyamoya | TIA, stroke, epilepsy, EEG, head CT/MRI, angiogram |
| | Renal transplant artery stenosis | Bruit, angiogram |
| | Tumors compressing on renal vessels | Angiogram |
| Endocrine | Catecholamine excess | |
| | Pheochromocytoma/paraganglioma | Flushing, diaphoresis, tachycardia, abdominal mass |
| | Neuroblastoma | Tachycardia, abdominal mass, CT/MRI, ↑ urine and serum catecholamines, biopsy |
| | Sympathomimetic drugs: phenylpropanolamine (decongestant), cocaine, amphetamine, phencyclidine, epinephrine, phenylephrine, terbutaline, monoamine oxidase-inhibitor with tyramine containing foods | |
| | Corticosteroid excess | |
| | Cushing syndrome: | Truncal obesity, moon facies, abdominal striae, hirsutism |
| | ACTH dependent | ↑ ACTH; brain MRI |
| | ACTH independent | ↓ ACTH; CT/MRI abdomen |
| | Mineralocorticoid excess | Ambiguous genitalia/virilization (girls), phallic enlargement/scrotal hyperpigmentation (boys); ↑ 17-hydroxyprogesterone |
| | Congenital adrenal hyperplasia | (21-hydroxylase deficiency); hyponatremia, hyperkalemia, FTT (boys) |
| | Aldosterone-secreting tumors | ↑ Aldosterone, ↓ PRA, hypokalemia, metabolic alkalosis |
| | Thyroid disease | Nervousness, exophthalmos (Graves' disease), muscle tremors, weight loss, heat intolerance, thinning skin/fine hair, frequent bowel movements; ↓ TSH, ↑ T4 |
| | Hyperthyroidism | |
| | Hypothyroidism | Fatigue, muscle cramps/weakness, weight gain, dry/coarse skin and thinning hair, cold intolerance, constipation; ↑TSH, ↓T4 |
| | Hypercalcemia (primary or secondary to malignancy, hyperparathyroidism, vitamin D intoxication) | |
| Cardiac | Coarctation of the aorta[a] | Radio-femoral delay of pulses, normal/low blood pressure in legs, heart murmur |
| | Mid aortic syndrome[a] | |
| Pulmonary | Obstructive sleep apnea | Snoring |
| | Bronchopulmonary dysplasia[a] | Supplemental oxygen requirement for >28 days in neonates (see ATS diagnostic criteria) |
| Central nervous system | Elevated intracranial pressure | Bradycardia |
| | Seizures | |

(*Continued*)

**TABLE 1** | Continued

| Organ system | Differential diagnosis | Findings/workup |
|---|---|---|
| Medications | Steroids | Moon facies, abdominal striae |
| | Immunosuppressants | |
| | Cyclosporine | Hypertriglyceridemia, hypertrichosis, gingival hyperplasia, hirsutism, headache, tremors, aphthous ulcers |
| | Tacrolimus | Hyperkalemia, hypomagnesemia, tremors, hyperglycemia |
| | Sirolimus | Impaired wound healing, dyslipidemia, myopathy, liver dysfunction |
| | Oral contraceptives | |
| | Anesthetics: ketamine | |
| | Erythropoietin | |
| Monogenic HTN | Liddle's syndrome | Hypokalemia, metabolic alkalosis, low PRA and aldosterone |
| | Gordon's syndrome (pseudohypoaldosteronism type II) | Hyperkalemia, low/low normal PRA and aldosterone |
| | Syndrome of apparent mineralocorticoid excess | Hypokalemia, metabolic alkalosis, low PRA and aldosterone, FTT, elevated ratio of urinary tetrahydrocortisol + allotetrahydrocortisol/ tetrahydrocortisone, hypercalciuria |
| | Glucocorticoid remediable aldosteronism (aka familial hyperaldosteronism type I) | Hypokalemia, metabolic alkalosis, normal/high urinary aldosterone, 18-oxo-tetrahydrocortisol/tetrahydrocortisol >1 |
| Miscellaneous | Post ECMO[a] | |
| | Cyclical vomiting syndrome | Vomiting, hyponatremia, migraines |

*Adapted from Kapur and Baracco (16) and Brady and Feld (14).*

[a]*Common etiology of HTN in neonates and infants.*

*ACTH, adenocorticotrophic hormone; ANCA, antineutrophil cytoplasmic antibody; ATS, American thoracic society; CAKUT, congenital anomalies of the kidney and urinary tract; CRP, C-reactive protein; CT, computed tomography; ECMO, extra-corporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; FTT, failure to thrive; HSP, henoch schonlein purpura; HUS, hemolytic uremic syndrome; MRI, magnetic resonance imaging; PAN, polyarteritis nodosa; PRA, plasma renin activity; SLE, systemic lupus erythematosus; TIA, transient ischemic attack; VUR, vesico-ureteral reflux; WBC, white blood cell.*

PGLs, all patients presented with polycythemia at birth or in early childhood (30). The earliest age of presentation with PCC/PGL was 8, with a median age of 17. Somatostatinomas developed in 5 of the 7 patients at a median age of 29 (range 22–38), and erythropoietin levels were about fivefolds above the upper limit of normal (ULN). Common ocular complications associated with this syndrome include dilated capillaries and fibrosis overlying the optic disk (31).

Multiple other gene mutations associated with hereditary PCCs and PGLs have been identified in the past decade and include TMEM127 involved in the mTOR pathway, MAX that controls gene transcription (32, 33) as well as KIF 1B, EGLN1, IDH1, and FH, with unclear clinical significance (34). **Table 2** lists the syndromic as well as newer gene mutations associated with PCCs and PGLs and describes the biochemical profile of such tumors, including the earliest age of presentation as noted in the literature.

Advances in molecular diagnostics have identified a distinction amongst hereditary PCCs and PGLs in the two different pathways that these tumors can fall under. The pseudohypoxic response usually stabilizes hypoxia-inducible factors (HIFs) under normoxic conditions. Gene mutations in VHL, SDHx, and HIF2 confer a reduced oxidative response with angiogenesis and hypoxia and encompass cluster 1 tumors. Conversely, kinase signaling in cells is usually kept at bay by various mechanisms as these promote cell proliferation, growth and survival dysregulation. Gene mutations in RET, NF1, KIF 1B, TMEM 127, and MAX were found to activate kinase signaling pathways leading to tumors with such features, termed cluster 2 tumors. In contrast, sporadic PCC/PGLs have features from both clusters (26). A 2017 retrospective study comparing pediatric and adult hereditary PCCs and PGLs demonstrated that cluster 1 tumors were more prevalent in the pediatric population by 76 versus 39% (40).

Malignancy rates vary and are estimated to be between 12 and 47% based on small case series (4, 6, 8, 41). In contrast, 10% of pediatric patients in the EAPPR had malignant tumors, none of which were of sporadic occurrence. Those with SDHB mutations had the highest prevalence for malignancy with extra-adrenal and thoracic paraganglial tumors posing additional risk factors (11, 42). Adult studies have also shown that SDHB mutation carry a higher risk for malignancy at 13–23% (43). The European-American-Asian Pheochromocytoma-Paraganglioma Registry prospectively followed up on predominantly adult patients with the newer gene mutations SDHA, TMEM127, MAX, and SDHAF2 and determined that 12% (4/34) of SDHA mutation carriers and 10% (3/29) of TMEM127 mutation carriers had malignant tumors (35). In contrast, of the small number of MAX mutation carriers, 9% (1/11) had a malignant tumor, with the only SDHAF2 mutation carrier being devoid of malignant disease. With regards to risk for malignancy, a single center retrospective review identified tumor size >6 cm in diameter, having a PGL or having a sporadic tumor as characteristics posing an increased risk for malignancy in a logistic analysis (4).

Twelve to sixty percent of tumors are extra-adrenal in location based on small case series (4, 6, 8, 17, 19) while the EAPPR had a rate of 30%, which may be a better reflection given the large amount of registrants. Bilateral adrenal tumors are reported to be present in 24–40% of pediatric cases (6, 8, 9, 11).

## Algorithm for Genetic Testing

While in the past one would consider the syndromes MEN2, VHL, NF1 or sporadic mutations as the cause of PCCs or PGLs,

**TABLE 2** | Clinical features of syndromes associated with pheochromocytoma (PCC) and paragangliomas (PGLs), as well as earliest age of diagnosis, malignancy rate, and additional information including hormone-secreting profile of tumors.

| Syndromes | Gene | Clinical features | Earliest age of diagnosis (year)[c] | Malignancy rate (%)[d] | Additional information |
|---|---|---|---|---|---|
| Multiple endocrine neoplasia type 2 | RET | | | 2.9 | |
| Type 2a | | Medullary thyroid carcinoma<br>PCC<br>Hyperparathyroidism<br>Cutaneous lichen amyloidosis | 5–8 | | PCCs are the first clinical manifestation in 10–30% of patients |
| Type 2b | | Medullary thyroid carcinoma<br>PCC<br>Multiple neuromas<br>Marfanoid habitus | 12 | | Penetrance of ~50%<br>Produce both epinephrine and norepinephrine<br>Bilateral in 50–80% of patients (3) |
| FMTC | | Familial medullary thyroid carcinoma | | | |
| Von Hippel–Lindau syndrome type 2 | VHL | | 5 | 3 (11) | |
| Type 2a | | Retinal and CNS hemangioblastomas<br>PCC (often bilateral)<br>Endolymphatic sac tumors<br>Epididymal cystadenomas | | | PCCs present in 10–20% of patients in adult series (3) versus 6–49% of pediatric cases (6, 9, 11, 17, 36)<br>Produce norepinephrine |
| Type 2b | | Renal-cell cysts and carcinomas<br>Retinal and CNS hemangioblastomas<br>Pancreatic neoplasms and cysts<br>PCC (often bilateral)<br>Endolymphatic sac tumors<br>Epididymis cystadenomas | | | |
| Type 2c | | PCC (often bilateral) | | | |
| Neurofibromatosis type 1 | NF1 | Neurofibromas<br>Café-au-lait spots<br>PCC<br>Lisch nodules<br>Optic pathway/CNS gliomas<br>GIST | 7 | 9.3–33 (11) | PCCs present in 4% (11)<br>Produce epinephrine and norepinephrine |
| **Paraganglioma–pheochromocytoma syndromes (SDHx)** | | | | | |
| | SDHA | Extra-adrenal paragangliomas (PGLs) (34) | 8 (35) | 0–14.3 | |
| PGL4 | SDHB | HNPGL[a]<br>PCC[b]<br>Extra-adrenal PGLs<br>GIST<br>Renal cell carcinoma | 6 | 17–30.7 (11) | SDHB mutation in 12.5–20% (11, 17, 36) pediatric cases<br>SDHD mutation in 10% pediatric PCC cases (11) |
| PGL3 | SDHC | HNPGL[a]<br>GIST | 12 | – | Produce norepinephrine and rarely dopamine |
| PGL1 | SDHD | HNPGL[a]<br>PCC[b]<br>Extra-adrenal PGLs<br>GIST<br>Papillary thyroid carcinoma (rarely) | 5 | 3.5 | |
| PGL2 | SDHAF2 | HNPGL | 15 | – | |
| Pacak–Zhuang syndrome (29) | HIF2A | HNPGL<br>Somastostatinoma<br>Polycythemia | 11–17 (30, 37) | – | Described in 4 pediatric patients |
| Syndrome not described | TMEM 127 (32) | PCC<br>HNPGL<br>Extra-adrenal PGLs | | 4.3–12 (35) | No pediatric case reports |
| Syndrome not described | MAX (33) | PCC (often bilateral) | 17 (33) | 9–25 (35) | Described in 1 pediatric patient |

*Adapted from Lenders et al. (3), Havekes et al. (1, 3), and Neumann and Eng (38).*

*CNS, central nervous system; HNPGL, head and neck paragangliomas; GIST, gastrointestinal stromal tumors; SDH, succinate dehydrogenase.*

[a]*More frequent in SDHD with a lifetime prevalence of ~90%.*

[b]*More frequent in SDHB with a prevalence of ~80% (data mostly derived from adult observations) (1).*

[c]*Adapted from Bausch et al. (11) and Waguespack et al. (39), unless otherwise specified.*

[d]*Adapted from Welander et al. (26) unless otherwise or additionally specified.*

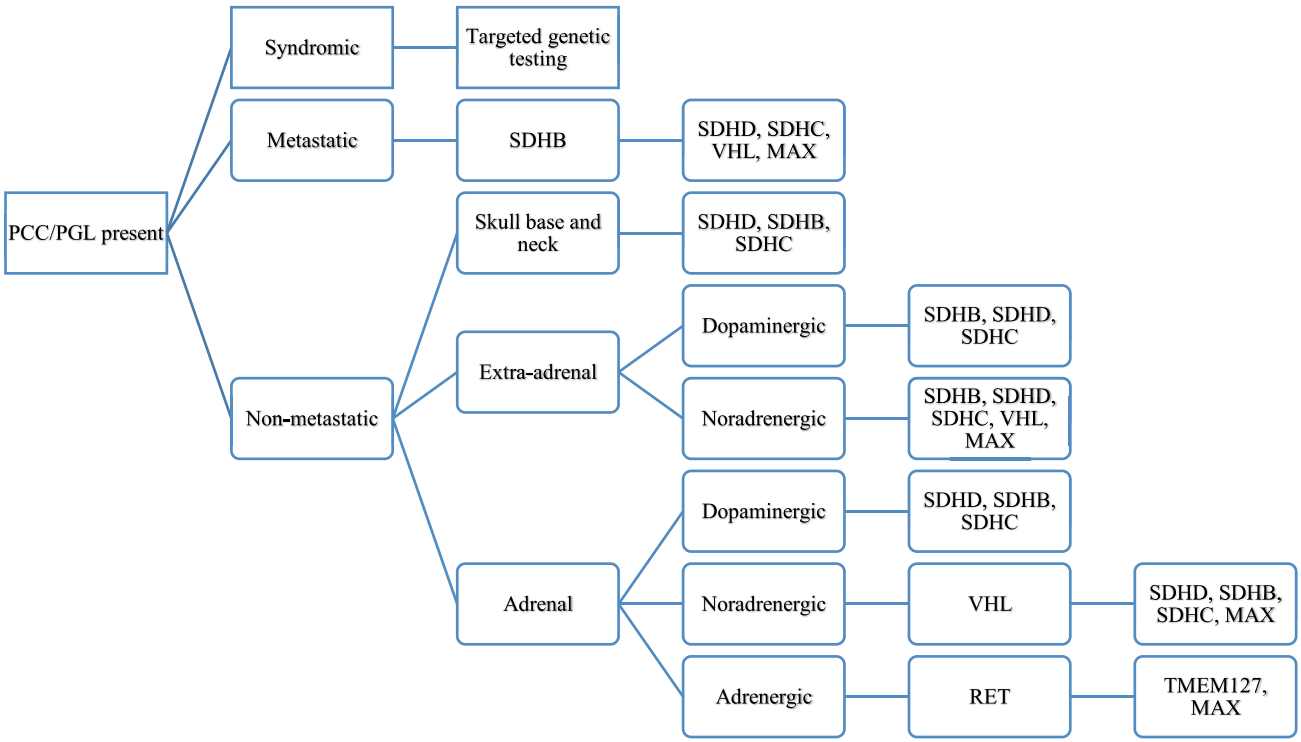


**FIGURE 1** | Proposed algorithm for genetic testing of patients with pheochromocytoma (PCC) or paraganglioma (PGL) based on patient's clinical characteristics, biochemical phenotype, and clinical aspects of the tumor. Reproduced with permission from Lenders et al. (45).

the discovery of new gene mutations that cause such tumors now needs to be incorporated into the diagnostic algorithm of patients thought to have a PCC or a PGL. An understanding of what constitutes a positive from negative staining of the SDHx genes is crucial to guide the clinician in the type of genetic testing to be performed. The SDHx subunits are found in mitochondria and exhibit a granular cytoplasmic pattern of staining if no mutation is present. Gill et al. demonstrated that SDHD mutations exhibit a weak diffuse staining pattern while SDHB mutations had a completely absent staining (44). Thus, a positive staining would entail intact SDHx subunits while a negative/weakly positive staining would indicate a mutation in the SDHx subunits (44). As can then be expected, syndromes that do not have a SDHx gene mutation, to include MEN II, VHL, and NF1, will stain positive for SDHx. **Figure 1** depicts a proposed algorithm for genetic testing on patients with hereditary PCC or PGLs.

# WORKUP

## Laboratory Testing

Laboratory testing should be undertaken once there is clinical suspicion for a PCC or PGL. Measurements of plasma and 24 h urinary catecholamines (epinephrine, norepinephrine, and dopamine) and urinary vanillylmandelic acid (VMA) have fallen out of favor due to lower sensitivity and specificity (**Table 3**), and assessing catecholamine metabolites is now recommended. These include plasma free metanephrines (metanephrine and normetanephrine) and 24 h urinary fractionated metanephrines (46). Metabolic processes unrelated to the tumor produce VMA, decreasing its sensitivity for diagnosis. Conversely, the production of plasma free metanephrines is constant and independent of the release of catecholamines, which is episodically secreted (47), making these the gold standard for diagnosis (46, 48). The degree of elevation of catecholamine metabolites (49) ought to be assessed when evaluating for catecholamine-secreting tumors, as shown in **Figure 2**. Values >4 times the ULN are highly suggestive of a tumor (49) while values >ULN and <4 ULN need to be investigated further as shown in **Figure 2**. One needs to take into account potential confounders, listed in **Table 4**, which may lead to false positive and false negative results of metanephrine testing. In cases of slight elevations in plasma catecholamine metabolites, the clonidine suppression test has been used in adults to help diagnose a neuroendocrine tumor, where suppression of ≥40% of plasma metanephrines signifies the absence of a tumor (45, 49).

Tumors can rarely secrete a predominance of dopamine; these are usually extra-adrenal PGLs with SDHx gene mutations (57). Since there is no definitive constellation of symptoms pointing to dopamine-secreting tumors, their detection depends on the measurement of the dopamine metabolites methoxytyramine and homovanillic acid (22). The utility of plasma methoxytyramine as a biomarker for metastatic PCCs and PGLs was described in 2012, where patients with metastatic tumors had a 4.7-fold higher plasma methoxytyramine level than those without metastatic tumors (58).

Chromogranin A (CgA), a protein present in chromaffin cells which controls secretion of hormones from secretory granules, may improve sensitivity of diagnosing SDHB and SDHD related tumors with concomitant use of plasma metanephrines (59). Sensitivities and specificities of CgA and plasma metanephrines were 73.2/95.9 and 70.7/98.6%, respectively, in SDHB mutation carriers with PCCs and sympathetic PGLs. Sensitivity of detecting such tumors was increased by 22% (from 70.7 to 92.7%) when CgA was used in conjunction with plasma normetanephrines in these SDHB-related tumors. With regards to metastatic disease within this cohort of patients, the use of CgA in addition to plasma metanephrines improved the sensitivity of diagnosis from 75 to 94.4%. CgA levels were not a sensitive marker for diagnosing HNPGLs, where the additive effect of CgA with plasma metanephrines provided a small increase in sensitivity of diagnosis of SDHD related tumors from 71.4% for plasma metanephrines alone to 78.6% for both biomarkers (59). However, this study was limited by a small number of patients with HNPGLs, with further conclusions to be determined after investigating this biomarker on a larger group of patients with HNPGLs. The results of this study suggest that initial elevations of CgA in patients with SDHB-related tumors allow the use of CgA as a biomarker for further follow-up. Some SDHB-related tumors have been found to be biochemically silent owing to the lack of the enzyme tyrosine hydroxylase (60); perhaps CgA may prove to be helpful in their diagnosis.

**TABLE 3** | Sensitivity and specificity of biochemical tests used in the diagnosis of pediatric pheochromocytoma.

| Biochemical test | Sensitivity (%) | Specificity (%) |
|---|---|---|
| Plasma normetanephrine and metanephrine | 100 | 94 |
| Plasma norepinephrine and epinephrine | 92 | 91 |
| Urinary normetanephrine and metanephrine | 100 | 95 |
| Urinary norepinephrine and epinephrine | 100 | 83 |
| Urinary vanillylmandelic acid | 63–75[a] | 94[a] |

*Adapted from Weise et al. (48), Ludwig et al. (17), and Pacak et al. (50).*
*[a]Sensitivity of 75% was from a pediatric series (17); sensitivity of 63% and specificity of 94% were from adult data (50).*

## Imaging

Localization of neuroendocrine tumors should be pursued with imaging once biochemical evidence is established (see **Figure 2**).

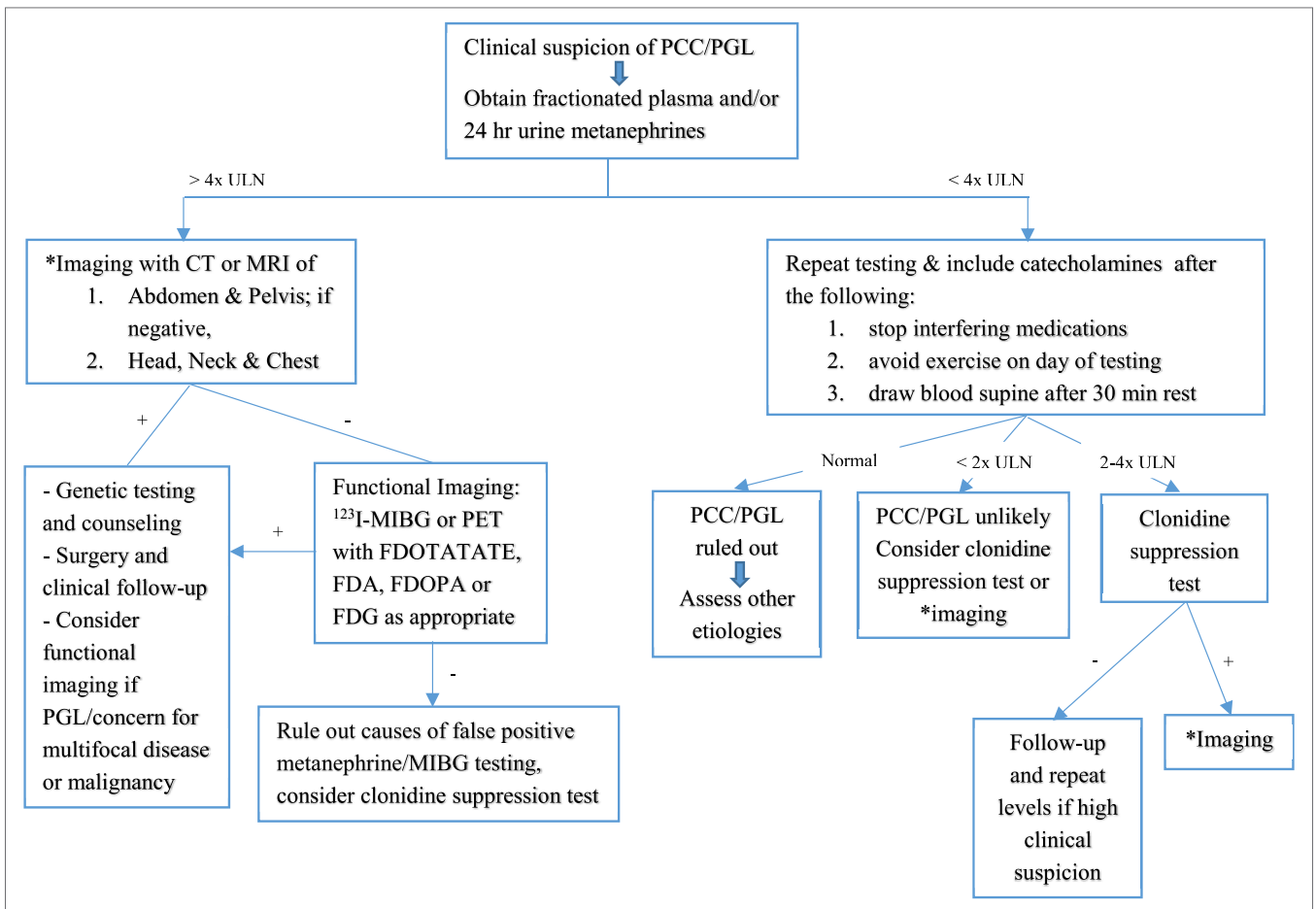


**FIGURE 2** | Flowchart for diagnostic algorithm for pheochromocytomas (PCCs) and paragangliomas (PGLs). +, positive; –, negative; ULN, upper limit of normal. Adapted from Waguespack et al. (39) and Dobri et al. (5).

**TABLE 4** | Factors associated with false positive and false negative testing of metanephrines.

| False positives |
|---|
| Medications (3) |
| Calcium channel blockers |
| Beta blockers |
| Mood stabilizers: tricyclic antidepressant, buspirone |
| Sympathomimetics: amphetamine, ephedrine |
| Stimulants: caffeine, nicotine |
| Dopaminergic agents: levodopa, alpha-methyldopa |
| Acetaminophen |
| Age |
| Increase in plasma metanephrines with age (51) |
| Posture |
| Increase in plasma metanephrines in seated versus supine position (52, 53) |
| Exercise (52) |
| High catecholamine diet (54) |
| Hypertension (3) |
| Obstructive sleep apnea (53, 55) |
| Stroke (3) |
| Renal impairment (56) |
| **False negatives** |
| Small tumors, usually <2 cm in size in normotensive patients being screened initially or for recurrence |
| Dopamine-secreting tumors |

Renal ultrasound as the first modality of choice will miss small adrenal tumors and PGLs due to sensitivity and specificity of 89% (61) and 61% (62), respectively. Hence, CT or MRI of the abdomen and pelvis have been the imaging modality of choice in numerous pediatric cases (4, 17, 19, 20, 36, 63) given similar diagnostic sensitivities (90–100%) (50, 64). Specificities of both are around 70–80% (50, 64). MRI has better sensitivity than CT to locate extra-adrenal tumors and can evaluate the extent of invasion into the spinal canal and involvement of major vessels (4). Some advocate for MRI over CT scan in children given radiation exposure with CT (1).

As neither study is as specific in discerning a PCC/PGL from other abdominal pathology, functional imaging studies need to be pursued if one has a high index of suspicion for PCCs or PGLs, if a PGL is detected or if there are concerns for multifocal disease or malignancy. These include $^{123}$metaiodobenzylguanidine ($^{123}$I-MIBG) scan, positron emission tomography (PET) with [$^{18}$F] fluorodopamine (FDA), [$^{18}$F] fluorodeoxyglucose (FDG), and [$^{18}$F] fluorodihydroxyphenylalanine (F-DOPA). $^{123}$I-MIBG scan has been used in conjunction with CT/MRI in some studies to locate and rule out multifocal disease (4, 17, 19, 20, 64), offering 95–100% specificity in localizing PCCs/PGLs (50). The adult literature describes malignant PCCs/PGLs that lose the ability to accumulate this isotope, making a MIBG scan potentially negative in such cases (3). One needs to be mindful that tricyclic antidepressants, CCBs, and BBs (3) and over the counter decongestants interfere with tumor uptake of the iodinated isotope used in MIBG scans and their use should be discontinued prior to obtaining MIBG scans. [$^{18}$F]-FDA PET has helped in defining and localizing tumor in a pediatric patient (65) and an adult patient with negative imaging but positive biochemical testing (66) and in the case of metastatic disease (3). In contrast, [$^{18}$F]-FDG PET has been the recommended functional imaging technique to evaluate malignant and metastatic PCCs/PGLs, particularly in SDHB mutation carriers in adults (67). Recent advances in functional imaging of PCCs/PGLs have led to the use of radiolabeled DOTA peptides, such as [$^{68}$Ga]-DOTATATE PET, which has high affinity for somatostatin receptor 2. Such receptors are known to be overexpressed in PCC/PGLs. Adult studies have demonstrated the superiority of [$^{68}$Ga]-DOTATATE PET in localizing metastatic SDHB-associated PCCs/PGLs over the other functional imaging studies, excluding MIBG (68). [$^{68}$Ga]-DOTATATE PET was also the most sensitive test in detecting HNPGLs (68, 69), especially SDHD tumors but inferior to F-DOPA PET/CT in detecting PCCs (69) in sporadic cases. Another study confirmed the high detection rate of PCCs/PGLs using [$^{68}$Ga]-DOTATATE PET but noted that [$^{18}$F]-FDG PET had higher uptake than the former in cases of mutations involving the pseudohypoxic cluster and a dedifferentiated tumor with loss of SSTR expression (70). In addition, CT with $^{123}$I-MIBG proved to have a lower lesion detection rate than [$^{68}$Ga]-DOTATATE PET and [$^{18}$F]-FDG PET in identifying PCCs and PGLs (70).

# MANAGEMENT

## Preoperative

Preoperative management of neuroendocrine tumors is crucial to prevent intraoperative complication of a hypertensive crisis. There has been a drastic decrease in perioperative complications from 45–69 to 3% with the use of alpha blockade (20, 63, 71, 72). Beta blockade is instituted following alpha blockade to offset reflex tachycardia from alpha-2 receptor antagonism and should never precede alpha blockade. This is due to the likelihood of causing a severe hypertensive crisis from unopposed alpha-receptor stimulation. Medications used preoperatively are discussed below with a goal BP reduction of <50 percentile for age and height. Dilated cardiomyopathy can develop from chronic catecholamine-induced hypertension, making an echocardiography valuable preoperatively (73, 74). One pediatric case report discusses the utility of pulmonary artery monitoring to assess fluid status in this setting, which has been described in adults (75).

Patients are asked to consume a high sodium diet of 6–10 g and fluid intake of at least 1.5 times maintenance a day once on an alpha blocker, to prevent hypotension from its vasodilatory properties (17, 36, 76). High fluid intake aids in expanding the contracted intravascular volume and reduces postoperative hypotension (77).

Patients are admitted to the hospital 24–36 h prior to surgery and given an alpha blocker, beta blocker, and in some cases a tyrosine hydroxylase inhibitor, the night before surgery (17, 36, 72, 78). Intravenous fluids of normal saline are given at 1.5 times maintenance to prevent hypotension prior to surgery (17, 36). **Table 5** provides a list of medication regimens used in pediatric catecholamine-secreting tumors, with further information delineated as follows.

### Alpha Blockers

Phenoxybenzamine, a non-competitive alpha-1 and 2 adrenoreceptor antagonist, has been widely used since the 1950s to control

**TABLE 5** | Drugs used in preoperative blockade of pediatric catecholamine-secreting tumors.

| Class of drug/drug name | Starting dose | Maintenance dose | Common side effects |
|---|---|---|---|
| Non-selective alpha blocker<br>Phenoxybenzamine | 0.2 mg/kg/day (max. 10 mg/dose) | Increase by 0.2 mg/kg/day every 4 days to goal<br>0.4–1.2 mg/kg/day ÷ every 6–8 h (max. 2–4 mg/kg/day) | Orthostatic hypotension<br>Tachycardia<br>Nasal congestion |
| Selective alpha-1 blocker<br>Doxazosin | 1–2 mg/day | Increase to 4–16 mg[a], daily or ÷ 2 times daily | Orthostatic hypotension<br>Dizziness |
| Non-selective beta blocker<br>Propranolol | 1–2 mg/kg/day, ÷ 2–4 times daily | 4 mg/kg/day, up to 640 mg/day, ÷ 2–4 times daily | Dizziness<br>Fatigue<br>Asthma exacerbation |
| Selective beta-1 blocker<br>Atenolol | 0.5–1 mg/kg/day, daily or ÷ 2 times daily | 2 mg/kg/day, up to 100 mg/day, daily or ÷ 2 times daily | Edema<br>Dizziness<br>Fatigue |
| Alpha and beta blocker<br>Labetalol | 1–3 mg/kg/day, ÷ 2–3 times daily | 10–12 mg/kg/day, up to 1,200 mg/day, ÷ 2–3 times daily | Dizziness<br>Fatigue<br>Asthma exacerbation |
| Tyrosine hydroxylase inhibitor<br>Metyrosine | 20 mg/kg/day, ÷ every 6 h<br>OR<br>125 mg daily | Increase up to 60 mg/kg/day ÷ every 6 hrs<br>OR<br>Increase by 125 mg every 4–5 days to max. 2.5 g/day | Orthostatic hypotension<br>Diarrhea<br>Sedation<br>Extra-pyramidal symptoms<br>Crystalluria[b] |

[a]*This study did not differentiate if the maximum dose of 16 mg was used in both pediatric and adult patients; however, review of pediatric dosing of doxazosin suggests a maximum dose of 4 mg/day. Titrating drug dosage to effect is recommended.*

[b]*Rare but potential side effect; with doses greater than 2 g/day, daily urine volume exceeding 2 L is recommended per manufacturer's guidelines.*

hypertension preoperatively. Doxazosin or prazosin, competitive alpha-1 adrenoreceptor antagonists, are used by some adult centers since they do not cross the blood–brain barrier as does phenoxybenzamine, precluding central symptoms like headaches or nasal stuffiness (78). Reflex tachycardia is avoided with no alpha-2 adrenoreceptor blockade. The shorter duration of action of doxazosin or prazosin leads to little to no postural hypotension preoperatively, favoring their use in some adult case studies (78, 79).

Given the rarity of neuroendocrine tumors in pediatric and adult patients, there are no randomized controlled trials looking at the subtypes of medications. Numerous small pediatric case studies relate their experiences with preoperative management (4, 17, 36). Romero et al. delineated a stepwise approach to managing pediatric patients with neuroendocrine tumors (36). Phenoxybenzamine is given at a starting dose of 0.2 mg/kg/day once daily (max 10 mg/dose), increasing by 0.2 mg/kg/day every 4 days to reach a maintenance dose of 0.4–1.2 mg/kg/day divided every 6–8 h (max 2–4 mg/kg/day) 7–10 days prior to surgery (36).

Doxazosin has been used in children in a series of 50 patients, with a starting dose of 1–2 mg up to 16 mg, given daily or divided twice daily (18). Of note, this series also comprised adults, and the authors did not distinguish if the higher doses were used in pediatric patients.

The adult literature reviewed the efficacy of preoperative phenoxybenzamine, doxazosin, and prazosin in terms of having fewer hemodynamic fluctuations intraoperatively. A retrospective study showed no difference (80), a prospective study showed superiority of phenoxybenzamine over prazosin (76), and a retrospective study showed superiority of doxazosin over phenoxybenzamine (81).

## Tyrosine Hydroxylase Inhibitor

Monotherapy with an alpha blocker has been found to cause hemodynamic instability intraoperatively during tumor manipulation. Metyrosine, a tyrosine hydroxylase inhibitor, prevents catecholamine synthesis and has been used in adults to prevent intraoperative BP fluctuations (79). The combination of phenoxybenzamine or prazosin and metyrosine in adults resulted in better BP control pre- and intraoperatively, with less need for pressure agents intraoperatively than when using phenoxybenzamine alone (79).

Ludwig et al. used metyrosine in 40% of their pediatric cases with 16% (one case) experiencing hemodynamic lability intraoperatively versus 50% (three cases) in those who did not receive this medication ($P = 0.54$) (17). They note their experience to be in agreement with the adult literature that metyrosine use is associated with a decreased need for intraoperative vasoactive medications, fluids, and decreased blood loss.

Perry et al. conducted a retrospective chart review of 25 adult patients with PCC, some of which received metyrosine in addition to phenoxybenzamine (72). Although there were no significant differences in BPs pre-, intra- and postoperatively, careful review of patients showed that those who received metyrosine had more severe disease and more stable BPs intraoperatively. Those who received the combination had less blood loss and less need for intraoperative fluids.

The pediatric literature does not have a consensus on the dosage of metyrosine. In addition to Ludwig et al. who used metyrosine, there are two case reports on children with catecholamine-secreting tumors who received metyrosine. The first dates back 24 years and used metyrosine in an 11 kg, 18-month-old child at a starting dose of 20 mg/kg/day divided every 6 h, titrated up to 60 mg/kg/day divided every 6 h (82). The other dates back 30 years and used metyrosine in a 12-year-old girl,

weight ~30 kg. The starting dose of 125 mg daily was titrated up by 125 mg every 4–5 days to a maximum dose of 3.5 g daily (83). Metyrosine dose was reduced to 2.5 g after the patient experienced multiple oculogyric crises and received metyrosine for roughly 6 months, following which she underwent surgery. Most recent literature by Ludwig et al. (17) does not discuss the dosage or length of metyrosine used in pediatrics. In adults, dose of metyrosine starts at 250 mg every 6 h, titrated up by 250–500 mg daily to a maximum dose of 4 g/day, given 8–14 days prior to surgery (72, 79).

Based on the above data, pediatric dosing of metyrosine should start at either 20 mg/kg/day divided every 6 h, or 125 mg daily, whichever comes first based on the patient's weight then titrated to maximum dose of 2.5 g daily over at least 8 days. The clinician should be mindful of the side effect profile of this medication (see **Table 5**), as well as signs of overdose to include persistent fatigue, anxiety, decreased salivation, dry mouth, diarrhea, and neuromuscular effects (tightening of the jaw, fine tremor of hands, and gross tremor of trunk), which may prompt reducing dose to prior step. This drug is available in 250 mg capsules, which can be opened and mixed to provide dilutions as appropriate for pediatric patients.

### Beta Blockers

Beta blockers are generally used after alpha blockade has been instituted, to suppress reflex tachycardia. Standard pediatric dosing can be started at least 3 days prior to surgery (36) and should never be initiated prior to alpha blockade as this can lead to a hypertensive crisis. Tumors secreting primarily epinephrine (78) cause tachycardia and require a beta blocker.

## Intraoperative

There has been a shift in surgical expertise when resecting neuroendocrine tumors from laparotomy to laparoscopy in the adult (84, 85) and pediatric population (86, 87). Laparoscopic resection and adrenal cortical-sparing procedures are now the preferred approach, the latter being important in patients with bilateral adrenal disease, to preclude cortisol deficiency. Additional points of consideration in performing cortical-sparing surgery are the risk of disease recurrence, high malignancy rate and the likelihood of a patient to not require corticosteroids (88). Between 15 and 30% of the adrenal gland is needed to preserve function (89) and this, including the above points, should help in the decision tree to perform cortical-sparing surgery (88). Intraoperative hypertension is controlled with a variety of agents including sodium nitroprusside or esmolol (36). Magnesium sulfate, dexmedetomidine, or nicardipine have also been used (36, 75, 90). Care should be exercised when giving fluids intraoperatively if patients are hypotensive, to preclude cardiopulmonary complications in the case of catecholamine-induced cardiomyopathy (74, 77). Given the potential complications of resecting such tumors, an experienced anesthesiologist and endocrine surgeon are essential to the care of these patients.

## Postoperative

The use of phenoxybenzamine is associated with postoperative hypotension from sustained alpha blockade for the 24 h following surgery. This can be resistant to adrenergic arteriolar constrictors and instead requires intravascular fluids to maintain hemodynamic stability (78, 80). Postoperatively the sustained alpha blockade was not seen in patients receiving doxazosin as compared to phenoxybenzamine (78). Hypoglycemia can occur postoperatively due to rebound hyperinsulinism from a reduction of catecholamines and should be monitored (91).

## Treatment of Malignant PCCs and PGLs

Complete surgical resection is the curative therapy of PCCs and PGLs; in the instance of malignancy, certain therapies can offer disease control. $^{131}$I-MIBG is currently used for malignant tumors and relies on the uptake of MIBG by the norepinephrine transporter. If tumor uptake of this radioisotope is poor, other modalities to include peptide receptor radionuclide therapy with radiolabeled somatostatin analogs or $^{111}$In-pentetreotide scintigraphy (SRS) may be performed (92). Chemotherapy with cyclophosphamide, vincristine, and dacarbazine are also utilized with malignant disease in both pediatric and adult cases. The largest study to date has shown progressive disease in 52% (11 patients), while 4% (1 patient) had complete remission, 22% (5 patients) had partial response, and 22% (5 patients) had stable disease (93). Finally, external beam radiotherapy (EBRT) has been used to control metastatic PCCs and PGLs, with results of the largest retrospective study of 24 patients indicating symptomatic control in 81% of lesions and stable disease in 87% of lesions (94). A retrospective review of 17 patients with PGLs excluding HNPGLs were treated with EBRT with 76% of the patients achieving either local disease control or symptomatic relief (95). The retrospective nature of both studies does not allow for the determination of long-term disease progression or stability when using EBRT and hence prospective studies would be helpful.

# SURVIVAL, RECURRENCE, AND LONG-TERM FOLLOW-UP

A retrospective chart review of 30 pediatric patients, from 1975 to 2005 showed that those who were classified as having benign disease had a 100% survival rate as compared to those with malignant disease, who had 5-, 10-, and 15-year survival rates of 78, 62, and 31%, respectively (4). Genetic testing was not available during that time period except for five patients who tested positive for a RET mutation (three patients) or an SDHD or SDHB mutation (two patients). Authors from this study classified malignant disease as that with distant metastases, tumor unresectable due to local invasion of vital structures or tumor recurrence regionally or distally after initial resection and initial negative microscopic margins. Ludwig et al. reported on a 100% overall survival rate and 95% 5-year disease free survival, based on the lower malignancy rate of 7% in their patient population and their ability to achieve negative microscopic margins in all resections (17). Recent survival data from the EAPPR of the patients who were diagnosed in the pediatric age group show that 6% (8 patients) of those with hereditary disease (144 patients) died, with a follow-up mean range of 10–19 years (range 0–53 years) (11). Three of the patients had VHL, three had SDHB mutations, two had NF1, and one SDHA with the cause of

death being metastases in seven and cardiac failure in one patient. All 33 patients with sporadic disease, followed for a mean of 10 years (range 1–45 years) were alive at subsequent follow-ups. The overall mean life expectancy of hereditary disease was 62 years. Life expectancy was greatly reduced with SDHB-associated disease, at 47 years, while patients with VHL had the lowest life expectancy at 27 years.

Malignant PCCs and PGLs are defined by the World Health Organization classification as the presence of metastases that does not include local invasion of a tumor (96). As such, a malignant tumor that has not yet metastasized may be classified as benign. Two classification systems exist to predict malignant potential of PCCs and PGLs. The PCC of the Adrenal Gland Scaled Score (PASS) (97) utilizes the histologic pattern, degree of cellularity, presence of necrosis, type of invasion and mitotic features to classify tumors while the Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) (98) additionally takes into account the Ki67 proliferation index of tumors as well as their biochemical profile. As user variability exists in the PASS system, it is not used in most centers. On the other hand, the GAPP system needs to be validated before being implemented into clinical practice. Given the lack of reliable markers to distinguish a benign lesion from a malignant one, lifelong follow-up of patients is required in the instance that metastases develop.

Long-term follow-up of these tumors is essential due to recurrence, which has been noted to occur anywhere between 1 and 14 years following initial presentation (11, 99, 100) in small pediatric case series. In contrast, data from the EAPPR showed that 38% of the pediatric registrants ($n = 177$) had recurrences after a mean time period of 25 years (11), with a reported recurrence rate of 12–38% (4, 11, 18, 100). The incidence of recurrent tumors increased with time, from 25% at 9 years to 50% at 31 years (11). The types of recurrent tumors were extra-adrenal (18%) and contralateral (13%) (95% CI 31–46) more so than ipsilateral (16%) ones (95% CI 12–28%) (11). Recurrences were significantly more common in patients with germline mutations than those with sporadic disease and tended to recur 10 years earlier, with a latency period of 23 versus 33 years, respectively (11). The mutations seen with these recurrent tumors were associated with VHL and SDHD mutations. Within these gene-specific mutations, SDHD mutations had a recurrent tumor after 18 years of latency versus 21 years for VHL mutations. HNPGLs recurred in 4% of pediatric patients and were caused by SDHD mutations at initial diagnosis and during recurrences. Seven percent of patients had a third recurrence, with a time interval of 1–20 years (mean 5 years) from second to third tumor; they all had germline mutations. The prevalence of malignancy was highest in SDHB mutation-positive individuals, with extra-adrenal and thoracic PGLs posing added risk for malignancy (11).

In a retrospective study of 263 patients with PCCs or PGLs, 125 were found to have metastatic disease, of which 32 patients presented before 20 years of age (42). Of those, 72% (23 patients) had a germline mutation in SDHB, 9.4% (3 patients) had an SDHD mutation, and 6.3% (2 patients) had a VHL mutation, with the absence of a known mutation in the remainder (4 patients). The study that established plasma methoxytyramine as a biomarker for metastatic PCCs and PGLs also recognized the association between extra-adrenal disease, tumor size >5 cm and SDHB mutation carriers associated with a high risk of malignancy (58).

Long-term follow-up on patients with hereditary PCCs and PGLs cannot be stressed enough given the lifelong risk of recurrence and metastatic disease. Laboratory testing with serum/urine metanephrines should be performed yearly and patients should undergo imaging studies intermittently and as clinically indicated based upon symptoms and/or positive laboratory testing (17) at follow-up visits. Smaller pediatric and adult case series recommend follow-up at 6 weeks and between 6 months and 1 year following initial surgery, then annually (17, 50).

The different characteristics of known mutations may change the follow-up frequency and surveillance emphasis. For example, SDHB mutations have high risk of metastasis (42), VHL and SDHD mutation carriers have high recurrence rates (11), and SDHA and TMEM127 have now been identified to confer added risks of malignancy. Recommendations of the EAPPR are to perform annual surveillance for the first 3 years after initial diagnosis of mutation carriers, this being the time frame where malignancy is apparent unless diagnosed at presentation, followed by lifelong follow-up. However, since malignancy can occur much later in life, constant and frequent follow-up is advisable in such patients.

## CONCLUSION

Pheochromocytoma and PGL, although rare, are potentially curable causes of secondary hypertension in pediatric patients. The identification of new gene mutations and the determination of recurrence and malignancy rates have allowed clinicians to acquire a better understanding of this disease process. All patients should be offered genetic testing given the high rate of inheritance of these tumors in pediatrics. All patients with genetic mutations should be followed throughout their lifetime given the risk of recurrence and malignancy. Those with SDHB gene mutations ought to be aggressively followed given the high risk of metastatic disease. Precise management of hypertension in such patients allows for safe pre-, intra-, and postoperative courses. It should be stressed that a multidisciplinary approach is needed in the treatment of patients with PCC or PGL. A team of experienced nephrologists, endocrinologists, genetic counselors, radiologists, endo-oncologists, oncologists, and surgeons will allow for optimal delivery of care to such patients and will also allow for the orchestration of follow-ups and careful attention to the recurrent and malignant potential of these tumors.

## AUTHOR CONTRIBUTIONS

RB created the outline, performed a literature review, and wrote the manuscript; TB contributed expert knowledge and experience and edited the manuscript.

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MINI REVIEW
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# Left Ventricular Hypertrophy in Pediatric Hypertension: A Mini Review

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Adults with arterial hypertension (HTN) have stroke, myocardial infarction, end-stage renal disease (ESRD), or die at higher rates than those without. In children, HTN leads to target organ damage, which includes kidney, brain, eye, blood vessels, and heart, which precedes "hard outcomes" observed in adults. Left ventricular hypertrophy (LVH) or an anatomic and pathologic increase in left ventricular mass (LVM) in response to the HTN is a pediatric surrogate marker for HTN-induced morbidity and mortality in adults. This mini review discusses current definitions, clinically relevant methods of LVM measurements and normalization methods, its epidemiology, management, and issue of reversibility in children with HTN. Pediatric definition of LVH and abnormal LVM is not uniformed. With multiple definitions, prevalence of pediatric HTN-induced LVH is difficult to ascertain. In addition while in adults cardiac magnetic resonance imaging is considered "the gold standard" for LVM and LVH determination, pediatric data are limited to "special populations": ESRD, transplant, and obese children. We summarize available data on pediatric LVH treatment and reversibility and offer future directions in addressing LVH in children with HTN.

**Keywords: left ventricular hypertrophy, LVMI, target organ damage, childhood hypertension, cardiac magnetic resonance, echocardiography**

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## INTRODUCTION

Framingham Heart Study proved that adults with arterial hypertension (HTN) have increased mortality due to myocardial infarction and stroke compared to adults without HTN.[1] These "hard outcomes" have not been clearly demonstrated in children with HTN. However, the Bogalusa Heart Study showed that children with HTN become hypertensive adults and that the major etiologies of adult heart disease (atherosclerosis, coronary heart disease, essential HTN) begin by 5–8 years of age.[2] Since there are no "hard outcomes" of the deleterious effects of HTN in children, they are assessed by the "end organ" or "target organ" damage (TOD). Pediatric HTN-induced TOD manifests as an injury to several organs: (A) kidney: microalbuminuria/proteinuria, chronic kidney disease (1, 2), (B) eye: retinopathy (3), (C) vessels: increase in intima media thickness, atherosclerosis,

[1] www.framinghamheartstudy.org.
[2] www.clersite.org/bogalusaheartstudy/.

reduced arterial compliance (2), (D) brain: cognitive impairment (4), and (E) heart: left ventricular hypertrophy (LVH) (5). TOD associated with uncontrolled HTN leads overtime to "hard outcomes" observed later in life (6). However, if HTN is controlled at least some of the TOD has been shown to be reversible (1, 7). Therefore, it is of paramount importance for pediatricians to be able to recognize presence of TOD as early as possible to act on it and thus prevent one of the "hard outcomes" in adulthood. LVH independently of blood pressure (BP) levels predicted poor prognosis in adults enrolled in the Framingham Heart Study. The relative risk of cardiovascular mortality for every 50 g increment in left ventricular mass (LVM) was 1.73 in men and 2.12 in women (8). The focus of this mini review is on definition, detection, epidemiology, management, and reversibility of LVH.

## DEFINITION

Left ventricular hypertrophy is defined as an increase in LVM in response to a disease state, due to either increase in left ventricular (LV) wall thickness or an increase in cavity size or both. These changes of LV diameters represent adaptive responses to a pathologic workload due to HTN or heart valve disease (as oppose to physiologic states of pregnancy or exercise/cardio-workout). However, LVH could also be related to infiltrative diseases of the myocardium or certain genetic disorders. HTN-induced LVH in children usually presents with an increase in wall thickness (concentric hypertrophy), without an increase in cavity size (eccentric hypertophy). Concentric LVH induced by HTN leads with time to LV dilatation, which results in a decline of the LV ejection fraction and eventually in "dilated cardiac failure" (9). Widening of the LV chamber creates circulatory difficulties and presents a vicious cycle to the cardiac muscle, increasing risk for cardiovascular complications (10). Both casual office BP readings and 24-h ambulatory blood pressure monitoring (ABPM) have a direct relationship to LVM/LVH: the higher office BP, the higher average BP recorded over the course of the day and night, or the higher ABPM BP loads (prevalence of abnormal elevated BP readings) the greater possibility for LVH (11). It is worth noting that long-standing white-coat HTN (normal ABMP and abnormal office BP) is associated with increased risks of cardiovascular complications in adults (12). However, this relationship is not consistent in number of pediatric patients with white-coat HTN (13). In summary, the definition of pediatric HTN-induced LVH pivots on an accurate assessment of LVM and determination of what normal versus abnormal is for a given individual. This in turn depends on the accuracy of LVM measurements, and LVH detection and normalization method used.

## DETECTION METHODS

### Cardiac Magnetic Resonance (CMR)

Cardiac magnetic resonance uses strong magnetic fields that stimulate the hydrogen nuclei (present in water or fat) to release radio waves that can be interpreted by computerized scanners and generate images of the heart (14). In adults, CMR imaging is considered as the gold standard for assessment of LVM and LVH (15, 16). In addition, CMR estimates of LVM have been shown to be closely correlated to actual heart weight determined at autopsy in both animal and human models (16). CMR yields high-quality images across the entire left ventricle that is not impeded by thoracic fat deposits and chest wall expansion. Furthermore, CMR is used in the evaluation of congenital heart disease, ant its use has been recently reported in children and young adults on maintenance dialysis (17, 18), and renal transplant recipients (19). Our group has described the utility of CMR in overweight hypertensive children and reported reproducibility (20). However, CMR is not yet widely available, is more expensive than echocardiography (ECHO), has disadvantages such as claustrophobia and the need for sedation in small children, and the data on its utilization in general pediatric population with HTN are lacking. Abnormal LVM and LVH in pediatric CMR is defined as a *z* score greater than +2.0 utilizing published review that calculated and tabulated pooled weighted mean values that are specific for age and sex (21).

### Echocardiography

Although LVM determined by CMR is more accurate and reproducible, ECHO has lower cost and is a more accessible test compared with CMR. ECHO is an imaging technique that creates pictures of the heart utilizing high-frequency ultrasound waves. Whether it be two-dimensional, three-dimensional, or M-mode, ECHO is used to assess TOD and measure LVM. Echocardiographic studies determine the myocardial volume by subtracting the LV cavity volume from the volume of the correspondent epicardium. Upon obtaining the myocardial volume, multiplication by the myocardial density results in the LVM (22). The LVM can then be indexed to body surface area (BSA), or height$^{2.7}$ to determine LVH (23). One of the challenges when using echocardiographic techniques to determine LVH is precisely finding the boundary between the cardiac blood pool and the endocardium (23). If this step was inaccurate due to, for example, poor acoustic window, or abundant chest fat tissue, there would be improper readings of the LV cavity volume and the epicardial volume. This in turn would result in inaccurate myocardial volumes when performing calculations and thus, inaccurate LVM levels and LVH indicators. For adults, a LVM index $\geq$51 g/m$^{2.7}$ is used to define LVH based on a study by de Simone et al., which showed LVMI above this threshold is associated with more than four times increased risk of morbidity and mortality (24). The Fourth Report selected 51 g/m$^{2.7}$ as their LVMI limit value to define LVH in children (25). However, this value does not adjust for growth and other potentially confounding factors. The Bogalusa Heart Study demonstrated that somatic growth is the strongest predictor of LVM (26). Therefore, LVM must be indexed to normalize the relationship without disregarding obesity. Foster et al. showed that normalizing LVM to BSA or height results in either underestimation or overestimation of LVM, respectively (27). They proposed lean body mass (LBM) as the ideal scaling variable for normalization. Although LBM can be measured by dual-energy X-ray absorptiometry, it is clinically difficult to ascertain (27). Foster et al. used LBM predictive equations and generated sex-specific LVM-for-LBM centile curves for

children 5–18 years of age and defined LVH as LVMI-for-age >95th percentile (27). Despite this, most pediatric nephrologists index LVM to height$^{2.7}$. Khoury et al. developed age- and sex-based LVMI (height$^{2.7}$) centiles in 2009 (28). They observed little variation beyond age 9, suggesting their reference tables would only be needed for younger children. They defined LVH as LVM/height$^{2.7}$ greater than 95th percentile for sex and age (28). According to their calculations after age 9 years, a constant 95th percentile value of 40 g/m$^{2.7}$ (female), and 45 g/m$^{2.7}$ (male) defines LVH (28). At present, it is challenging to say which indexing method is better because there is no one method without substantial limitations. Furthermore, ECHO cannot distinguish small but clinically significant changes in diastolic wall thickness from measurement error in individual children, even when measured by the same observer (29). Three-dimensional ECHO has also been utilized to quantify LVM and allows for LVM quantification using principles similar to CMR. LVM is determined by taking the difference between epicardial and endocardial volumes and may better account for ventricular morphology. Quantification of LVM by three-dimensional ECHO has been shown to be of use in the adult population; however, its use remains limited in pediatrics at this time (30).

## Electrocardiography (ECG)

There is no explicit ECG pattern predictive of abnormal LVM. Instead, there are host of electrical abnormalities (voltage and non-voltage criteria) that are associated with LVH. The most commonly used are the Sokolow–Lyon criteria (31), and voltage criteria must be accompanied by non-voltage criteria to be considered diagnostic of LVH (32). However, HTN-induced LVH could be easily misclassified by using ECG; therefore, ECG should not be used alone in determining presence or absence of LVH. However, ECG still has a place in TOD assessment as it gives independent information on the cardiovascular risk even after adjusting for LVM (32). In children with HTN, although ECG has high specificity (>90%), it is a poor screening test with low sensitivity (<35%) in evaluation of abnormal LVM (33).

Left ventricular hypertrophy detection methods summary is presented in **Table 1**.

**TABLE 1 | Summary of pediatric LVH clinical detection methods.**

| Method | Advantage | Limitation |
|---|---|---|
| ECG | – Availability (office/ emergency room)<br>– Low cost<br>– Minimal time requirement<br>– No need for sedation in small children<br>– High specificity (>90%) | – Poor sensitivity (<35%)<br>– No explicit ECG pattern predictive of LVH |
| ECHO M-mode | – 1st method of ECHO validated<br>– Relatively simple and quick<br>– Cost efficient<br>– Superior endocardial definition<br>– No need for sedation in small children | – Measures LV in one dimension<br>– Assumes an ellipsoid LV shape with a ratio of long:short axis lengths of 2:1<br>– Relies on linear measurements of LV thickness, which, when cubed, increase the SD by a factor of 2–3×<br>– Debated accuracy and reproducibility |
| ECHO 2D | – More accurate and reproducible than the M-mode method<br>– Relatively simple and quick<br>– Cost efficient<br>– No need for sedation in small children | – Assumes an ellipsoid LV shape and a uniform LV wall thickness<br>– Prone to error mathematical formulae to estimate the LVM (without cube function = less error than M-mode) |
| ECHO 3D | – Improved the intra- and interobserver variability as compared to M-mode and 2D ECHO<br>– Does not rely on geometrical assumptions for calculating LVM<br>– Correlates well with CMR | – More complicated and expensive equipment<br>– Superior-quality 3D images are dependent on optimal echo windows (impaired in obese subjects)<br>– Lack of pediatric data |
| CMR | – "Gold standard" in selected populations<br>– Excellent the intra- and interobserver variability<br>– Independent chest wall thickness | – Requires sedation in small children<br>– Not widely available<br>– Lack of pediatric data in general population<br>– More expensive than ECHO |

*ECG, electrocardiography; ECHO, echocardiography; M-mode, motion (over time) mode; 2D, two-dimensional ECHO; 3D, three-dimensional ECHO; CMR, cardiac magnetic resonance; LVH, left ventricular hypertrophy; LVM, left ventricular mass.*

## Epidemiology

The prevalence of LVH in children and adolescents is not precisely known partly because multiple definitions in different population exist. It varies from 4.8 to 50% in children with primary HTN (27, 28, 34–36) and has been reported as high as 55% in children after renal transplant (37) and 85% in children on dialysis (38). In children with chronic kidney disease, the following factors contribute to abnormalities in calculating LVM: male sex, higher body mass index, degree of anemia, fluid overload, and low-grade inflammation and can be more relevant than the effect of HTN (39).

In pediatric essential HTN, severe LVH defined as LVMI above 51 g/height$^{2.7}$ has been found in 10–15% (34, 40, 41). The prevalence of LVH in children without HTN is unknown. In adults, it has been reported that obesity had significant independent associations with LVM and wall thickness (42), and this relationship has been confirmed in obese children and adolescents with normal office BPs (43, 44). In addition to body mass index, ethnicity contributes to differences in prevalence of LVH. A collaborative study of the International Pediatric Hypertension Association found that LVH and concentric hypertrophy occurred most frequently in hypertensive Hispanic children (35). In adults, LVH is more common in hypertensive African-Americans (AA) (50%) than in whites (33%) (45), and the adjusted risk of having LVH, whether indexed by height$^{2.7}$ or by BSA, is greater for AA than for whites (46). In AA children with HTN, LVH prevalence was 49 versus 30% among non-AA ($p < 0.05$) (36). Children of AA descent with chronic kidney disease and high-risk *APOL1* genotypes have both higher prevalence of LVH (53 versus 12%, $p < 0.01$) and obesity (48 versus 19%, $p = 0.01$) than their non-AA counterparts (47). Women were thought to have a lower prevalence of LVH than

men for any given level of BP (8). However, LVH prevalence differences between sexes are dependent on LVM normalized to either height, height$^{2.7}$, or BSA. LVM was identical in men and women when using LV mass/fat-free mass as a partition value of 4.1 g/kg (48). Since high dietary intake of sodium is associated with increase in BP and elevated BP is associated with LVH (49), salt restriction is associated with decrease in the incidence of LVH (50). In children with chronic kidney disease, differences in LVH prevalence between girls and boys were also dependent on LVH definition. When LVH was defined by LVM indexed to height, girls had higher prevalence of LVH (16 versus 9%, $p = 0.01$); when LVH was defined by LVM relative to estimated LBM, prevalence of LVH was similar between girls and boys (18 versus 17%, $p = 0.92$) (51). It has been known that adults with diabetes mellitus have higher LV mass, independent of HTN (52, 53). Adult type II diabetics have significantly higher prevalence of LVH in hypertensive women (54). Similarly, diabetic children have significant changes in LV dimensions, and girls are more affected than boys (55). Finally, there is strong evidence for the genetic influence on LVH prevalence across several study designs, datasets and ethnicities (56–60), and several genetic conditions, i.e., hypertrophic cardiomyopathy, caused by mutations in sarcomere genes (61), and RASopathies are causally associated with LVH (62). However, specific genetic influences on prevalence of HTN-associated LVH are currently unknown.

## Management and Reversibility

Hypertension is a rare cause of heart failure in children and adolescents. In children, the rationale to treat LVH is based on adult data. Special attention should be given to children and adolescents with HTN and the following conditions: end-stage renal failure, diabetes, coarctation of the aorta, or Kawasaki disease. These patients are at increased risk of early cardiovascular events and heart failure (63). Non-pharmacologic hypertensive treatments such as dietary salt restriction, weight reduction, avoidance of smoking, and aerobic exercise have been effective in lowering cardiovascular risk factors in adults (64). In children with HTN, if BP does not improve by lifestyle modification or there is evidence of TOD, then pharmacologic treatment is indicated (65). In children with HTN, presence of LVH prompts treatment and LVH reversal becomes a major treatment goal. The baseline severity of LVH, and the degree and duration of HTN control determines slope of LVH reversal (40, 66, 67). In adults, any BP lowering agent lowers the risk of LVH (68). All anti-HTN classes are effective in lowering of BP in children; however, their differential effects on LVH have not been demonstrated in pediatric population (25). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are especially effective in the regression of LVH due to host of additional BP-independent mechanisms: reduction of growth factors (TGF-beta), free oxygen radicals, inhibitory effects on myocyte growth, and collagen formation. In adults, treatment with ACE inhibitors or ARB increases insulin sensitivity (69, 70), whereas treatment with thiazides decreases insulin sensitivity (71, 72). In fact, ACE/ARB has been the drug of choice for over a decade for pediatric nephrologists who treat HTN (73). This preference comes not from pediatric data but from adult studies showing their beneficial, cardio and reno-protective effects in diabetes, HTN, and microalbuminuria (71, 72). In adults with HTN or with early-stage CKD, the addition of spironolactone to ACE/ARB reduced LVM and improved arterial stiffness (74). Spironolactone is usually used in children with congestive heart failure or as potassium sparring diuretic and not as first or second agent in HTN-induced LVH treatment. In adults, calcium channel antagonists are as effective as ACE inhibitors (such as Lisinopril) in their ability to reduce LVH and cardiac wall thickness (75). This is likely due to dominant effect of BP lowering over BP-independent effects. Another class of pharmacological agents that assist in the regression of LVH are beta receptor-blocking agents: both B1 receptor specific or non-selective that work through decreasing cardiac output and easing afterload facilitating LV remodeling. However, abnormalities in diastolic function associated with HTN-induced LVH are not reduced by reversal of LVH induced by antihypertensive treatment with beta-blockers (76). It is very interesting that in some children with primary HTN the main determinant of LVH regression is decrease in abdominal obesity with an increase in LBM rather than BP lowering (77). This conforms to recent adult study finding that higher BMI is associated with less reduction of hypertensive LVH: independent of BP control and of types of antihypertensive treatment (78). Although different classes of antihypertensive have different effects on LV mass in adults, the data regarding the specific effects of antihypertensive therapy on LVH in children are not adequate.

## Future Directions

Left ventricular mass and LVH are associated with HTN and with increased BMI. Efforts to diminish pediatric cardiovascular risk factors and prevalence of HTN-induced LVH should thus be connected to the public campaign to reduce obesity and increase childhood physical activity. In addition, emergence of effective approaches to issue of medication adherence may result in better long-term BP control. Recognition of food addictions, full understanding of sugar and food additives effects on anxiety, depression, BP, and hyperactivity may lead to effective interventions of addressing the root cause of obesity/HTN, which in turn may result with time in a decrease in the prevalence of LVH. Increased use of advanced technologies such as CMR or multidimensional ECHO should lead to improved detection of LVH and better understanding of its pathophysiology and epidemiology. Our improved understanding of cardiac electrogenesis and electrical remodeling in TOD may allow for more targeted treatment of electrical abnormalities associated with HTN. Furthermore, randomized controlled studies in pediatric HTN populations are needed to answer the question if available adult data can really be translated to children.

## AUTHOR CONTRIBUTIONS

RW wrote the mini review and contributed to review of literature and design of the review. AK, LP, and KS-M contributed to review of literature and wrote the part of the review.

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GENERAL COMMENTARY
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# Commentary: Left Ventricular Hypertrophy in Pediatric Hypertension: A Mini Review

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**Keywords: arterial hypertension, left ventricular hypertrophy, early diastolic alterations, prehypertension, tissue Doppler imaging**

**A Commentary on**

**Left Ventricular Hypertrophy in Pediatric Hypertension: A Mini Review**
*By Woroniecki RP, Kahnauth A, Panesar LE, Supe-Markovina K. Front Pediatr (2017) 5:101. doi: 10.3389/fped.2017.00101*

Woroniecki and colleagues' article on left ventricular hypertrophy (LVH) in pediatric hypertension (HTN) reviewed current definitions, clinically relevant methods of LVM measurements, and normalization methods as well as its epidemiology, management, and reversibility in children with HTN (1).

Since the publication in 1977 of the First American Task Force for the diagnosis, evaluation and treatment of high blood pressure (BP) in children and adolescents, updated in 1987, 1996, and more comprehensively in 2004 (as Fourth Report), the importance of HTN-related organ damage; in this context, LVH has been widely stressed. Likewise, the latest European Society of HTN guidelines for the management of HTN in children and adolescents published in 2016 has highlighted the assessment of subclinical organ damage as an intermediate stage in the continuum of vascular disease, targeting predominantly LVH (2).

Woroniecki and colleagues' article (1) exposed the puzzling concern of defining LVH in a pediatric population on the basis of the existence of diverse criteria with pros and cons. These arguments are not new and have contributed to the difficulty in recent years to ascertain a reliable standardization of LVH definition at the early stages of life in children and adolescents suffering from HTN. Although the authors of the article do not mention the connection of prehypertension with LVH, this association exists (3). Also long-established studies, conducted on hypertensive individuals (2), have reported different formulas to define LVH in children and adolescents.

These aspects complicate the resolution of a definition of LVH for prehypertensive patients.

Unquestionably, the search for a definition of LVH in the context of the issues raised in this commentary is complex with potentially multiple answers. To date, no outcome-based solution has been identified. Nevertheless, there is a reasonable expectation that some results will be forthcoming from the American Heart Association's SHIP-AHOY study, intended to evaluate BP thresholds, ambulatory BP, and metabolic phenotype that predicts hypertensive target organ damage. While SHIP-AHOY will definitely inform future guidelines, currently, after extensive review of 15,000 manuscripts; the new Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents (3) recommends using LVMI but does not address the different measures in the assessment of LVMI, although dictates to perform a first echocardiogram when considering BP medication initiation.

In our opinion, the appraisal of HTN-induced LVH must also include early diastolic alterations as regional mitral Ea, Aa, and the E/Ea ratio by Tissue Doppler Imaging that precede the onset of LVH (4). Those topics are not mentioned in Woroniecki and colleagues' article (1) and might be key

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to increasing the consistency of the assessment of HTN-related cardiac organ damage in children and adolescents.

The PESESCAD-HTA study found diastolic abnormalities even in prehypertensive adolescents without LVH, which underlines the relevance of targeting diastolic alterations on individuals prone to be hypertensive in the short term (5).

In short, the issue of LVH in pediatric populations remains challenging. The solution will require large multinational studies to find a more reliable and matching approach to determine the cardiac organ damage that HTN entails in children and adolescents.

## AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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REVIEW
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# The Microbiome and Blood Pressure: Can Microbes Regulate Our Blood Pressure?

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The surfaces of the human body are heavily populated by a highly diverse microbial ecosystem termed the microbiota. The largest and richest among these highly heterogeneous populations of microbes is the gut microbiota. The collection of microbes and their genes, called the microbiome, has been studied intensely through the past few years using novel metagenomics, metatranscriptomics, and metabolomics approaches. This has enhanced our understanding of how the microbiome affects our metabolic, immunologic, neurologic, and endocrine homeostasis. Hypertension is a leading cause of cardiovascular disease worldwide; it contributes to stroke, heart disease, kidney failure, premature death, and disability. Recently, studies in humans and animals have shown that alterations in microbiota and its metabolites are associated with hypertension and atherosclerosis. In this review, we compile the recent findings and hypotheses describing the interplay between the microbiome and blood pressure, and we highlight some prospects by which utilization of microbiome-related techniques may be incorporated to better understand the pathophysiology and treatment of hypertension.

**Keywords: hypertension, dysbiosis, microbiota, lifestyle, blood pressure, short-chain fatty acid, microbial metabolites**

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## BACKGROUND

The human microbiota is a mixed community of microorganisms composed of bacteria, viruses, archaea, and eukaryotic microbes that coinhabit the human body surfaces (1). The collection of those microbes and their genes is named the human microbiome (2).

Multiple studies have shown that each body site is characterized by unique ecological communities of microbial species (1) and each person has a unique microbiome (3). Those interpersonal variabilities are likely related to differences in our genetic background, origin, geographical location, age, life style, diet, and early exposure to various microbes, as well as exposure to antibiotics or probiotics (3). The microbiome composition is also affected by early life events; including delivery mode, gestational age, hospitalization, and the method of feeding (4).

Hypertension is a global public health problem and contributes to the burden of heart disease, stroke, kidney failure, premature death, and disability. It is considered the most prevalent modifiable cardiovascular disease (CVD) risk factor. High blood pressure affects 1.13 billion people worldwide. In the US, 75 million American adults (29%) suffer from high blood pressure, which is around one out of three adults (5). It is also estimated that more than 3% of children suffer from hypertension;

this number increases in obese children, since the prevalence of primary hypertension rises progressively with increases in BMI percentile from less than the fifth percentile (2%) to more than the 95th percentile (11%) (6). Globally, 42 million preschool children were overweight in 2013. The prevalence of obesity in the US is about 17%; it affects about 12.7 million children and adolescents (7, 8). It is important to mention that while obesity is associated with increased prevalence of hypertension, not all obese children are hypertensive.

Recently, multiple animal and human studies have examined the relationship between the gut and the oral microbiome and blood pressure (9–11). These studies aimed to explore different hypotheses linking the microbiota and its metabolites to blood pressure. Here, we provide an overview of the literature and discuss the proposed mechanisms. We also discuss potential microbiota-altering therapies and lifestyle modifications and their effect on blood pressure.

## THE MICROBIOME IN HEALTH AND DISEASE

Our microbiota is highly dynamic and continuously changing. This is in part a reflection of age-related changes like growth and development, where the highest variation takes place during childhood but later decreases with age (12). Newborns' and infants' microbiota differentiates and becomes distinct and site-specific as they grow older (13). The microbiota in infants less than 6 months old is different from that of older infants, where by the age of 3 years, a child's microbiome is highly similar to that of an adult and is considered relatively stable (14, 15). However, the microbiome composition remains subject to changes related to any disease, change of diet, use of antibiotics, and in response to major life events like pregnancy and puberty (16–18).

Microbiota composition is also determined by the physical characteristics and chemical properties of the site that is being colonized (19). Therefore, the primary determinant of community composition is the anatomical location: within the same habitat, interpersonal variation is significant (20) and is more complex than the temporal variability observed in multiple sites within the same individual (21). Those site-specific signatures of the microbiome help elucidate the many changes associated with health and disease.

### Tools Used to Study the Microbiome

Recent breakthroughs in high-throughput Next Generation Sequencing techniques, summarized in **Figure 1**, have leveraged our understanding of the composition and the function of the microbiome and have substantially advanced our knowledge on the crucial role of the microbiome in maintaining host physiology and homeostasis (22). Those techniques range from sequencing of the 16S rRNA-encoding genes, used to characterize the microbial phylogenetic composition of a sample collected from a specific body site, to the shotgun metagenomic approaches, used to identify all the genomes of microbes coexisting in the same site along with their biological functions (23–25). In addition to genomic sequencing-based analysis, other methods have been developed to study the microbial transcriptome, proteome, and metabolome, as they provide additional information at successive levels of microbial physiology (26). Metabolomics aim to study the metabolic functions by which the microbiota contributes to the human physiology; those functions include energy harvest, bile acid transformations, choline transformation, and the production of short-chain fatty acids (SCFAs), vitamins, and amino acids (27).

Those tools have tremendously contributed to our current knowledge about the microbiota and their metabolites (22, 27). In recent years, the microbiome was shown to constitute a unique "fingerprint marking" that may play a role in interindividual phenotypic variation in disease presentation, prognosis, progression, and even response to treatment (15, 20).

### The Gut Microbiome

Colonization of the human gut with a wide variety of microbes takes place just before birth as evident from the diverse microbial composition of the meconium (28). Maternal microbiota contributes to the formation of the first microbial inoculum, and then soon after birth, the microbial diversity increases and converges toward an adult-like microbiota by the end of the first 3–5 years of life (29). The ecosystem of an adult human gut contains a complex array of microbes with more than 100 trillion microbial cells and more than 1,000 bacterial species (30). The composition of the gut microbiota is highly variable between subjects, as each subject harbors a unique set of microbial species, which is in general highly stable over time in healthy individuals (31). A healthy human adult gut is dominated by the Gram-positive *Firmicutes* and the Gram-negative *Bacteroidetes* (31). Most nutrients consumed through a diet are processed by an array of various human enzymes before being absorbed by the small intestine; however, the gut microbiota contributes to the metabolism of dietary fibers that are not usually digested by those enzymes (32). In the large intestine, a group of microbes including clostridial clusters IV, XIVa, *Lactobacillus*, and *Actinobacteria* (*Bifidobacterium* spp.) contribute to the fermentation of dietary plant polysaccharides or fibers, indigestible oligosaccharides, non-digested proteins, and intestinal mucin in order to produce SCFAs (acetate, propionate, and butyrate) (33). In addition to its role in food digestion, the gut microbiota plays a vital role in inhibiting pathogen-invasion by creating colonization resistance, it also contributes to the education and stimulation of the immune system, maintenance of the intestinal epithelial homeostasis and integrity, synthesis of vitamin B and vitamin K, as well as the enhancement of the motility and function of the gastrointestinal tract (GIT) (31).

### The Oral Microbiome

The oral cavity is considered one of the most highly dynamic ecosystems in the human body (34–36). 16S rRNA gene sequencing estimated 50–100 billion bacteria in the mouth, comprised of nearly 700 identified bacterial species (36–38). Up to 80% of oral bacteria are dominated by about 200 species of *Firmicutes* and *Proteobacteria*, along with *Bacteroidetes*, *Actinobacteria*, and *Fusobacteria* totaling upwards of 95% of all identified oral microbiota (36–38). Further diversity exists between the varied niches of the mouth (34), such as the tooth surface, gingiva, hard and

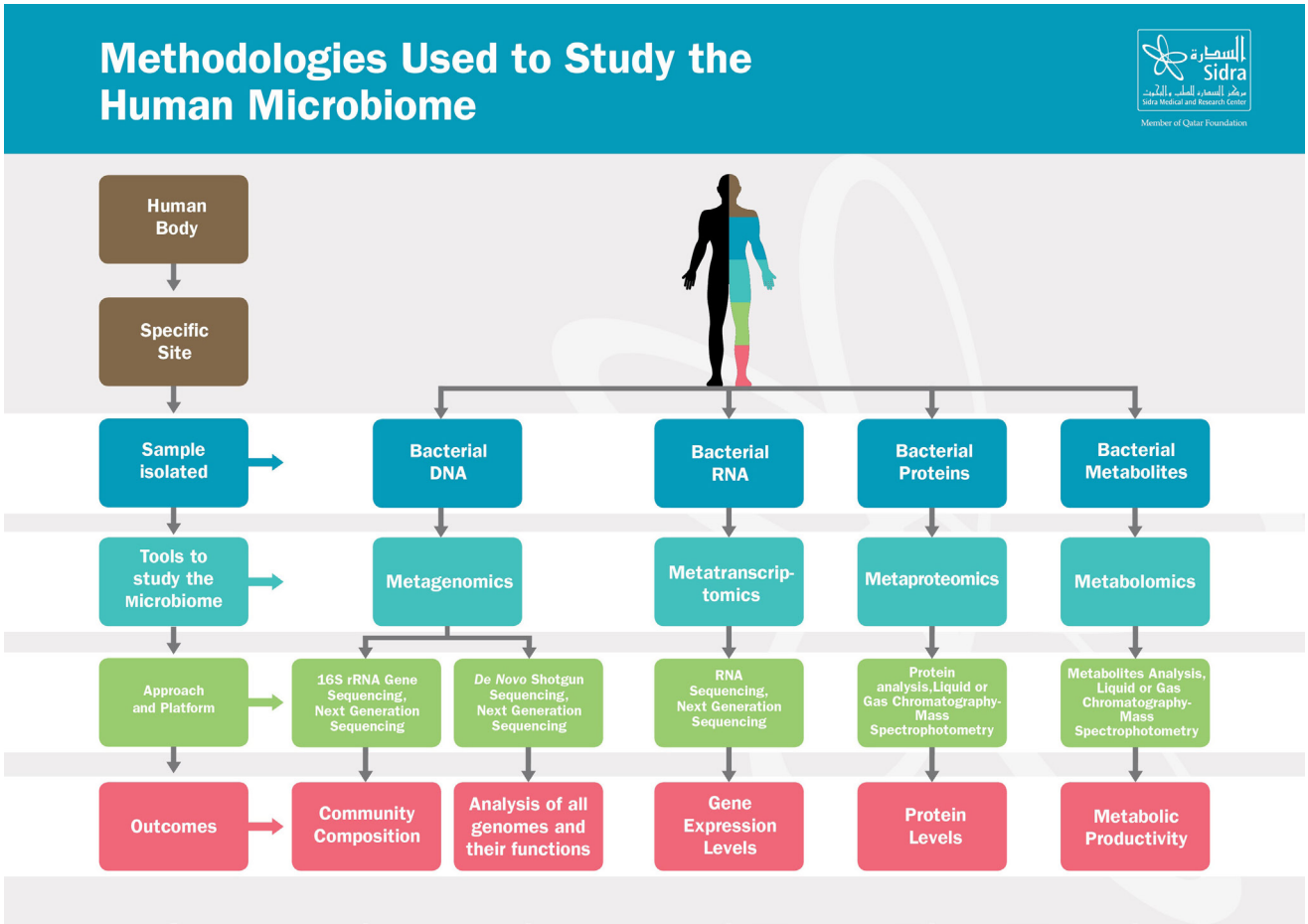


**FIGURE 1** | Methodologies used to study the human microbiome. The human body harbors large amounts of microbes that vary from one site to another. From each specific site, microbes can be studied in various ways depending on the samples isolated. Those tools range from metagenomics, metatranscriptomics to metaproteomics and metabolomics. Based on the approach and platform used, results include composition of the microbial communities, microbial genes function, gene expression or proteins levels, and metabolites activities.

soft palate, and even regionally on the tongue (34). Within this complexity, an ever-growing number of specific microbial taxa have been associated with both oral and systemic diseases (39). For instance, saccharolytic (sugar metabolizing) bacteria, such as *Streptococcus* and *Lactobacillus*, have been associated with dental caries, while proteolytic (protein metabolizing) bacteria, such as *Prevotella* and *Porphyromonas*, have been associated with periodontitis and halitosis (40). Presence of *Porphyromonas gingivalis* is shown to be associated with atherosclerosis (41), smoking (42), and several cancers (43).

## Microbial Dysbiosis and Disease

Dysbiosis is defined as the change in the composition and structure of the human microbiota of a given site, a change that may help explain why some individuals are more likely to develop certain diseases or develop a more severe form of the illness (44).

Although the relationship between microbial composition and stability to disease predisposition is not a cause-and-effect relationship, the microbiome is a contributor in many disease states, a link that has been previously overlooked. In fact, changes in the microbiome are increasingly linked to the development of several non-communicable diseases, including diabetes (45, 46), obesity (47), CVD (48, 49), cancer (50, 51), inflammatory bowel disease (IBD) (52, 53), asthma (54), and others. Recently, researchers have examined the relationship between kidney disease and the human microbiome, summarized in Ref. (55). Studies have shown a bidirectional relationship between chronic kidney disease and the gut microbiome; where microbiota-derived metabolites contribute to the progression of CKD and the state of chronic kidney disease and inflammation contributes to changes in the diversity and richness of the microbiota. Other studies showed differences in IgA disease progression and the gut microbiota composition, SCFA (derived from the microbiota) to modulate renal dysfunction in states of acute kidney injury *via* their anti-inflammatory properties, and kidney transplantation and immunosuppressive medications to significantly impact the gut microbiota composition.

It is, therefore, essential to understand the interface between the microbes and the host in any disease condition, as this may help uncover possible disease etiologies and pathogenesis. It may also be possible to use any novel microbial factors or host-related inflammatory markers as diagnostic and therapeutic targets for prediction, prevention, and treatment of some common diseases. Deciphering the possible interindividual variations in the microbial composition in various body sites and identifying the changes in site-specific microbiota composition during onset or progression of various diseases will help to pave the way toward developing microbiota-driven personalized medicine.

While large-scale studies addressed the role of the microbiome in some conditions including cancer, IBD, obesity, and diabetes, only fewer studies describing the role of the microbiome in regulating blood pressure have been published (10, 11, 56). Those studies suggested that hypertension is directly and/or indirectly linked to microbial dysbiosis, and that some microbial metabolites contribute to the regulation of blood pressure (10, 11, 56). Therefore, understanding the nature of hypertension-related microbial aberrations in various body sites may enable us to better understand the pathophysiology of high blood pressure and possibly develop personalized microbiome-based diagnostics for individuals at risk.

In this review, we discuss potential mechanisms by which the microbiota contributes to our blood pressure regulation and describe the link between dysbiosis and hypertension.

## HYPERTENSION AND THE MICROBIOME

Blood pressure regulation is complex. Multiple physiological systems interact, influenced by the environment and genes, to maintain blood pressure (57). These include but are not limited to: the renin–angiotensin–aldosterone system, the sympathetic nervous system (SNS), the nitrate–nitrite–nitric oxide signaling pathway (NO), uric acid, endothelin, the vasopressin system, natriuretic peptides, vasodilator peptides, the tissue kallikrein–kinin system, the immune system, the adipose tissue, and adipokines (58).

Recently, multiple animal and human studies have examined the relationship between the oral and gut microbiome and blood pressure; they demonstrated a significant decrease in microbial richness and diversity in the presence of hypertension. In addition, studies have demonstrated an altered microbial composition and modified metabolite profiles, suggesting a role for microbial dysbiosis and microbial metabolites in hypertension (11). In a rat model of hypertension, the number of cecal "good bacteria" from the phylum *Bacteroidetes* is reduced, which is accompanied by a proportional increase in the number of "bad bacteria" from the phylum *Firmicutes* (11). Studies have also shown that transplant of cecal microbial content from donor hypertensive animals can reproduce hypertension in previously normotensive recipient animals (56). A third set of studies demonstrated a beneficial effect for microbial mass reduction using antibiotics on blood pressure (11). Furthermore, absence of gut microbiota was found to protect mice from angiotensin II (AngII)-induced arterial hypertension, vascular dysfunction, and hypertension-induced end-organ damage (59).

The relationship between the microbiota and blood pressure is a complex one. Researchers have identified multiple possible hypotheses to link dysbiosis and hypertension. Many of which are indirect links that contribute to the metabolic syndrome and the overall increased cardiovascular risk. It is also important to point out that most of the studies were conducted in animal models, and many examined newly proposed hypotheses which yielded results that have yet to be reproduced. Some hypotheses focused on the association between microbial species in the microbiota and their relationship to blood pressure, whereas other hypotheses examined the role of dysbiosis in the pathogenesis (e.g., increased SNS activity), sustenance (e.g., inflammation), and worsening/progression of hypertension (e.g., endothelial dysfunction and vascular remodeling). Here, we provide an overview of the proposed hypotheses linking the microbiota to blood pressure, **Figure 2**.

### Microbial SCFA Metabolites Regulate Blood Pressure *via* Olfactory Receptors

Researchers have described a less rich and diverse microbiota in hypertensive compared to control subjects (11). SCFAs are products resulting from fermentation of various nutrients by the gut microbiota and are later absorbed into the blood stream (60). Members of the olfactory signaling pathway are expressed in the human kidneys. Olfr78 is an olfactory receptor that mediates renin secretion after stimulation by SCFAs (61). Other SCFA receptors including Gpr41 and Gpr43 (also called free fatty acid receptor 3 or FFAR3 and FFAR2, respectively) are also expressed in the renal vasculature. Propionate administration to Gpr41-deficient mice induced blood pressure elevation, suggesting that Gpr41 is needed to counterbalance the pressor response to SCFA (10).

### Increased Risk of Atherosclerosis from Microbiota-Generated Trimethylamine-*N*-Oxide (TMAO)

Another indirect connection between the gut microbiome composition and hypertension derives from the role of the gut microbes in the metabolism of choline and phosphatidylcholine to trimethylamine (TMA), which is further metabolized to the pro-atherogenic species, TMAO (62). Koeth and colleagues showed that the metabolism of dietary L-carnitine, a TMA abundant in red meat, by the intestinal microbiota results in the production of TMAO and accelerates the development and progression of atherosclerosis in mice (62). Recently, a study in a healthy human volunteer showed that microbiota in the small intestine generated the phosphatidylcholine breakdown product TMA (63). The resulting TMAO was suppressed by topical-acting antibiotics (63). It is important to point out that this link is with atherosclerosis and not directly to hypertension.

### Microbiota-Induced Neuroinflammation and Increased Sympathetic Activity

Vagal nerve stimulation and blocking sympathetic derive prevent breakdown of the intestinal lumen–blood barrier and enhance epithelia cell barrier function (64, 65). Santisteban and colleagues hypothesized that hypertensive stimuli (such as Ang II, salt, and

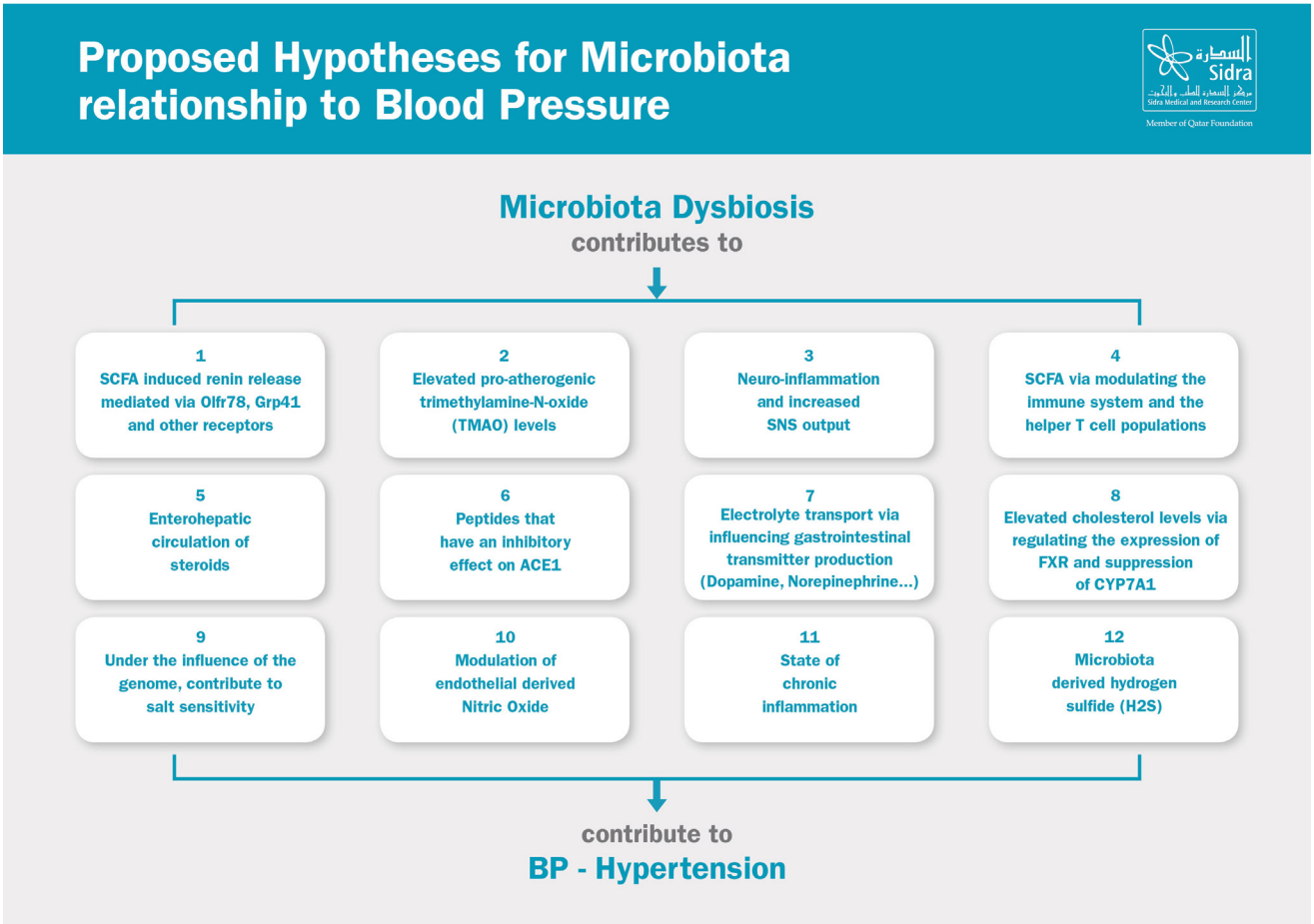


**FIGURE 2** | Proposed hypotheses for microbiota relationship to blood pressure. SCFA, short-chain fatty acids; SNS, sympathetic nervous system; ACE, angiotensin-converting enzyme; FXR, farnesoid X receptor.

stress) trigger autonomic neural pathways resulting in increases in sympathetic and dampening of the parasympathetic activities which in turn contribute to the overall increase in blood pressure (66). Increased sympathetic nervous activity to the gut could result in increased gut permeability, gut inflammation, and dysbiosis, leading to an imbalance in the microbial-derived metabolites in the plasma, possibly contributing to chronic inflammation and sustained hypertension.

## Modulation of Blood Pressure *via* the Effects of the Microbiota on the Immune System

Researchers have proposed a brain–gut–bone marrow axis in which sympathetic activity to the bone marrow induces mobilization of hematopoietic stem cells (66). In this hypothesis, hematopoietic stem cells may migrate to the brain or to the gut and contribute to local inflammation and immune responses. This may further increase the sympathetic activity and contribute to blood pressure elevation. On the other hand, SCFAs, such as acetate and butyrate, have been shown to have anti-inflammatory effects on myeloid and intestinal epithelial cells (67). Recently, Kim and colleagues reported marked decreases in microbial richness and diversity in hypertensive patients and also observed marked differences in circulating inflammatory cells in hypertensive individuals compared to controls (68); T-helper 17 cells were particularly relevant because activation of these cells is regulated by gut-intrinsic mechanisms, and their increase may be a result of dysbiosis in hypertension (68). In germ-free mice, the absence of gut microbiota seems to protect the animals from AngII-induced arterial hypertension, vascular dysfunction, and hypertension-induced end-organ damage. This protection appears to be mediated by inhibiting the accumulation of the inflammatory myelomonocytic cells in the vasculature and altered cytokine signaling (59).

## Role of the Microbiota in the Enterohepatic Circulation of Steroids

Another intriguing hypothesis involves the role of the gut microbiota in the enterohepatic circulation of steroids. Using antibiotic therapy, the bacterial flora of rats was modified to interrupt the enterohepatic circulation of steroids excreted in bile. Antibiotic and corticosterone were administered simultaneously to these

animals. After 5 days, rats receiving both steroids and antibiotics had an average elevation of 9.2 mmHg in their blood pressure compared with 24.6 mmHg in rats given steroid alone. These findings are consistent with the possibility that metabolites of steroids, when reabsorbed in the enterohepatic circulation, contribute to the physiological response to exogenous steroids (69). Further studies are needed to examine the role of gut-derived steroids.

## Inhibition of Angiotensin 1-Converting Enzyme

Nakamura and colleagues (70) reported a significant decrease in the systolic blood pressure in rats fed sour milk (contains the two tripeptides Val–Pro–Pro and Ile–Pro–Pro). Research on the health effects of pasteurized sour milk, which is fermented by a starter culture containing *Lactobacillus helveticus* as the predominant microorganism, indicated that antihypertensive effects and angiotensin-I converting enzyme inhibitory peptides are present in sour milk (71, 72). On the other hand, researchers have shown ACE2 has a RAS-independent function, regulating intestinal amino acid homeostasis, expression of antimicrobial peptides, and the ecology of the gut microbiome (73).

## Electrolyte Transport *via* Influencing Gastrointestinal Transmitter Production

The gut microbiota can influence the ability of the gastric and intestinal enterochromaffin cells to produce serotonin, dopamine, and norepinephrine. These transmitters have been found to influence Na–K ATPase and electrolyte transport in the intestine (74). It is still unclear whether enterochromaffin cell-derived transmitter effects are clinically significant in blood pressure regulation. Further studies are needed to examine the role of gastrointestinal transmitter production on blood pressure regulation.

## Elevated Cholesterol Levels *via* Regulating the Expression of RXR and Suppression of CYP7A1

Cholesterol is the precursor to bile acids synthesis in the liver. Bile acids are further metabolized by the gut microbiota into secondary bile acids. In the ileum and liver, nuclear farnesoid X receptor (FXR) plays a key role in the bile acid synthesis; when activated, it exerts negative feedback to control bile acid synthesis (75). Gut microbiota may indirectly play a role in the increased risk of atherosclerotic disease by increasing cholesterol levels; this may be attributed to its role in reducing the levels of tauro-beta-muricholic acid, a FXR antagonist, as well as by suppressing the rate-limiting enzyme CYP7A1 in bile acid synthesis from cholesterol (75). It is important to point out that this link is with atherosclerosis and increased cholesterol levels and not directly to hypertension.

## Under the Influence of the Host Genome, Microbiota May Contribute to Salt Sensitivity

Mell and colleagues hypothesized that the interaction between the host and the gut microbiota influences the development of salt-sensitive hypertension (76). They reported differences in the gut (cecal) microbiota composition between the salt-sensitive (S) and the salt-resistant (R) Dahl rats. After a single bolus of R rat cecal content to S rats, they showed exacerbated hypertension in high salt-fed S rats, with systolic blood pressure to be consistently and significantly elevated during the rest of the recipient rat life, which also had a shorter lifespan. They speculated that this effect may be mediated *via* SCFAs, as both acetate and hetanoate were higher in the R to S transfer group (76).

## Modulation of Endothelial-Derived Nitric Oxide (NO)

It is also worth mentioning that the nitrate–nitrite–nitric oxide signaling pathway involved in the pathogenesis of hypertension is highly affected by microbial diversity through the formation of nitrite, NO, and other bioactive nitrogen oxides (77). NO is an endogenously produced, lipophilic, and diffusible molecule that exerts a diverse array of critical autocrine and paracrine signaling activities. NO acts directly on smooth muscle cells to promote relaxation and inhibits both platelet function and vascular smooth muscle cell proliferation and migration (78). Formation of nitrite and propagation of its downstream NO-signaling effects depend on the oral bacterial reduction of inorganic nitrate by a set of bacterial nitrate reductase enzymes that are largely absent from the human genome (77, 79, 80). Studies in Sprague-Dawley rats (77) and normal human volunteers (81) showed that depletion of oral bacterial nitrate reductases by chlorhexidine mouthwash correlated with a 90% decrease in oral nitrite levels in humans, along with a 25% decrease in plasma levels ($p = 0.001$), and 2–3.5 mmHg increase in blood pressure (81). Several studies in hypertensive, overweight, and other patient populations have been performed, all revealing predictable acute or chronic blood pressure reduction with varying types of nitrate supplementation (82), this beneficial effect is abolished both acutely and chronically by antimicrobial mouthwash use [reviewed in Ref. (83, 84)].

## State of Chronic Inflammation

Dysbiosis, gut wall inflammation, and increased gut wall permeability have been shown to contribute to the state of chronic systemic inflammation. Endotoxemia has been linked to the development of low-grade systemic inflammation and vascular inflammation *via* toll-like receptor-dependent mechanisms (85). In obese individuals, intestinal microbiota composition was associated with local and systemic inflammation (elevated C-reactive protein) (86).

## Microbiota-Derived Hydrogen Sulfide ($H_2S$)

Microbiota, like many mammalian cells and tissues, also produce $H_2S$ (87). Microbes exploit this gaseous molecule as an antioxidant defense mechanism, for energy production, and for cell cycle regulation. It is estimated that 50% of fecal $H_2S$ is derived from bacteria, thus the total plasma $H_2S$ pool varies depending on the individual's microbiota milieu in the gut. $H_2S$ plays a crucial role in a variety of physiological functions, including smooth muscle relaxation, oxidant regulation, inflammation, and angiogenesis (88). Hydrogen sulfide is synthesized

primarily from the amino acids cysteine and homocysteine. $H_2S$ biosynthesis deregulation, particularly in the renal vasculature, may play a role in hypertension or possibly contribute to existing high blood pressure (89). Although theoretically plausible, it is unknown to what extent does microbiota-derived $H_2S$ contribute to blood pressure regulation in humans? This area is still in need of further research.

## HYPERTENSION EFFECTS ON THE MICROBIOTA COMPOSITION AND FUNCTION

While the focus of most studies was to examine how the microbiota at different body sites can modulate blood pressure, a few studies looked at the other direction of this relationship, that is, can hypertension affect our microbiota composition and cause dysbiosis? Is dysbiosis a target organ injury due to hypertension? And does dysbiosis precede, accompany or result from hypertension? It is important to point out that the majority of published studies were cross-sectional and were designed to examine associations and not to determine cause-and-effect relationships. Hypertensive animals and humans were found to have decreased microbial richness, diversity, and composition (11). Santisteban and colleagues tested the hypothesis that increased sympathetic drive to the gut in hypertensive animals is associated with increased gut wall permeability, increased inflammatory status, and microbial dysbiosis (90). Changes in gut pathology were present and were associated with alterations in microbial communities relevant to blood pressure control. However, whether gut permeability and dysbiosis played a role in the pathogenesis of hypertension or were a consequence of hypertension is still not clear. It is very well possible that the relationship between dysbiosis and hypertension is bidirectional or an amplifying one. Further studies are needed to decipher this relationship.

## ANTIHYPERTENSIVE MEDICATIONS: GUT MICROBIOTA-MEDIATED DRUG INTERACTIONS

The hepatic enzyme system is the key player when it comes to drug metabolism; however, the gut bacteria also exert a variety of metabolic changes to orally ingested drugs, including reductive and hydrolytic reactions. Researchers have reported gut microbiota-mediated drug interactions between multiple medications and antibiotics (91). Those interactions were mediated by alterations in the gut microbiota. The drug amlodipine's plasma concentration area under curve was increased by up to 133% in ampicillin-treated rats. This increase in its bioavailability was attributed to the reduction of gut microbiota that usually contributes to amlodipine metabolism (92). The authors went on to caution clinicians regarding the use of antibiotics in patients treated with amlodipine. On the other hand, antibiotic treatment alone using minocycline was able to "rebalance" the microbiota and was associated with blood pressure reduction (11). Another aspect to the interaction between antihypertensive medications and the microbiota was described by Santisteban and colleagues (90). In their study, they found increased permeability and stiffness of the gut barrier, decreased levels of tight junction proteins, increased gut fibrosis, thickening of the gut muscularis layer, decreased villi length, and goblet cell loss in spontaneously hypertensive rats and in rats with AngII-induced hypertension. Treatment of SHR with captopril reduced gut permeability and completely restored fibrosis levels and thickness of the muscularis layer and only partially restored villi length (90). Some studies are underway (clinical trial NCT02188381), and more are needed to further examine the microbiota interaction and its role in the metabolism of different antihypertensive medications, as well as the effect of concomitant antibiotic treatment.

## RESTORING THE BALANCE: CURRENT AND POTENTIAL INTERVENTIONS

Lifestyle changes and dietary interventions are key modifiable factors in the management of hypertension. Recently, researchers have started to examine changes in blood pressure as they manipulate the microbiome by introducing dietary and lifestyle changes.

### Lifestyle Modifications and Their Effect on Hypertension and the Microbiome

Sufficient sleep is vital for maintaining physical and mental health. Chronic sleep deficiency is related to a wide variety of diseases, including CVD and metabolic disease (93). Epidemiologic studies have established the best amount of sleep for adults as approximately 7 h and that this range correlates best with a lower prevalence of CVD and reduced risk of hypertension (94). Lately an intricate, bidirectional relationship between sleep, circadian rhythms, and the composition of the microbiome in mice was described (95, 96). Benedict et al. showed that sleep deprivation induced changes in microbial families of bacterial gut species in humans (97). Furthermore, Durgan et al. established a link between gut dysbiosis and the development of obstructive sleep apnea-induced hypertension (56). On the other hand, Zhang et al. reported that sleep restriction over several consecutive days does not overtly influence the composition of the microbiome of either rats or humans (98). Further studies are needed to examine the triangular relationship between sleep (duration and quality), blood pressure, and the microbiome.

Sedentary lifestyle is linked to poor health, increased cardiovascular, and metabolic disease risk (99). On the other hand, exercise offers a protective effect; it has a positive effect on body composition, immunity, and cardiovascular health (94, 99). Exercise affects the gut microbiome composition (100). Athletes have a more diverse gut microbiota; Clarke and colleagues showed that a positive effect exists between physical activity, increased dietary protein, and the diversity of the gut microbiome (101). Furthermore, Allen and colleagues demonstrated that different exercise modalities (forced and voluntary) can evoke changes in richness and evenness in the microbiome at varying body sites (102). It remains unclear whether the effect of physical activity on the microbiome is independent of any accompanying adjustment of dietary intake (mainly protein) (100).

## Diet and Its Effect on Hypertension and the Microbiome

Multiple dietary components have been shown to affect blood pressure (103), and various studies have examined the effect of manipulating those components on the blood pressure (104). The Dietary Approaches to Stop Hypertension (DASH) diet is one of the interventions used to reduce blood pressure (98). This diet is rich in fruits and vegetables, as well as low-fat dairy, and at the same time has a low content of saturated and total fat (105). DASH-sodium trial demonstrated significant dose–response decreases in blood pressure when the DASH diet and sodium restriction were combined (105, 106). This reduction in blood pressure was accompanied by 30 and 20% risk reduction of CVD after a long-term follow-up for 15–20 years, respectively (107). It is possible that components (high fiber, dairy) of such interventions alter the microbiota in favor of a more balanced one and contribute to its blood pressure-lowering effects (70).

## Food Supplements and Their Effect on Hypertension and the Microbiome

### Prebiotics

Prebiotics are non-digestible food ingredients that escape digestion in the upper part of the GIT, only to be available for breakdown and fermentation by the gut microbiota within the lower parts of the GIT (108). Most prebiotics are derived from plants. Their role in lowering the CVD risk has been attributed to their ability to lower serum lipid and cholesterol levels (109). Population studies indicate that higher dietary fiber intake was significantly associated with a lower risk of obesity and hypertension (110). Another possible mechanism by which prebiotics could regulate blood pressure is through the attenuation of insulin resistance (111). Additionally, prebiotics have also been reported to reduce the risk of hypertension by improving the absorption of minerals such as calcium in the GIT (112).

### Probiotics

Probiotics are living microorganisms that confer a health benefit on the host when administered in sufficient amounts (113). Some probiotic strains exhibit antihypertensive effects: for example, consumption of a dairy product mixture, including *Enterococcus faecium* and two strains of *Streptococcus thermophiles*, for 8 weeks lowered systolic blood pressure (114). Administration of *Lactobacillus plantarum* 299v for 6 weeks was also found to reduce systolic blood pressure in heavy smokers (115). Furthermore, consumption of probiotics-fermented potato yogurt could reduce hypertension-induced cardiac myocyte apoptosis in hypertensive rats and, therefore, can promote cardiac protection against hypertension (116). *Lactobacillus casei* and *Streptococcus thermophilus* TMC 1543 were also proven to lower systolic blood pressure and risk factors that caused ischemic heart disease (117).

### Synbiotics

Synbiotics are nutritional supplements containing both probiotics and prebiotics in a form of synergy (118). Synbiotics improved survival and distribution of microbial supplements within the GIT by facilitating selective stimulation and activation of growth and metabolism of probiotics (118). Just like prebiotics and probiotics, synbiotics can modulate the gut metabolic activities without modifying the overall structure. Predominant strains of probiotics used in synbiotic preparations include Lacbobacilli, Bifidobacteria species, *Saccharomyces boulardii*, and *Bacillus coagulans*, whereas Oligosaccharides, inulin, and other dietary fibers from natural sources form the basis of the prebiotic component. It is worth mentioning that an animal study examining the role of the synbiotic dietary supplement of *Lactobacillus plantarum* HEAL19 together with fermented blueberry was not effective in lowering blood pressure in hypertensive rats (119). To our knowledge, there are no human trials evaluating the effects of synbiotics on hypertension, such trials are warranted.

### Xenobiotics

Xenobiotics are chemicals or substances that are foreign to an organism or biological system. They are not nutrients and enter the body through ingestion, inhalation, or dermal exposure (120). Xenobiotics have the potential to induce gut dysbiosis and influence disease states. Previously published reviews elegantly shed the light on potential mechanisms that link the human gut microbiome to the efficacy and toxicity of xenobiotics (drugs, dietary compounds, and environmental toxins), even after short periods of exposure (121, 122). However, more research is needed to understand the interactions between xenobiotics, blood pressure, and the gut microbiome.

### Fecal Microbiota Transplants (FMT)

In FMT, the fecal matter is collected from a tested donor, then blended with saline or other solutions, filtered, and drained and later administered to the recipient *via* colonoscopy, endoscopy, sigmoidoscopy, or enema.

As the use of FMT in the management of severe or recurrent *Clostridium difficile* infection is becoming well established (123, 124) and its use in the treatment of IBD, especially ulcerative colitis, is being intensely studied (125), FMT is being increasingly evaluated for use in other areas. Vrieze and colleagues reported improved insulin sensitivity by transfer of microbiota from lean donors to individuals with metabolic syndrome (126). This result gives hope that FMT may become part of treatment regimens for metabolic syndrome and resistant hypertension in the future. Studies have also shown that transplant of cecal microbial content from donor hypertensive animals can reproduce hypertension in previously normotensive recipient animals (56); whether this can be reproduced in humans and whether reverse transplantation will achieve blood pressure reduction in hypertensive subjects remain to be tested.

More work is required to establish the effect of FMT in resistant hypertension. This will include careful evaluation, screening and donor selection, transplant composition, as well as mode of delivery of the transplant (127, 128). Also, it is not known whether the microbiota manipulation can be sustained without continuous application or the need for a concurrent change in dietary or lifestyle habits.

## CONCLUSION

Studies have described how dysbiosis may modulate blood pressure and contribute to CVD. While most studies were performed using animal models, a few studies were conducted in adult hypertensive subjects and none were conducted in children. Given the differences in the gut microbiota composition between children and adults, there is a pressing need for more studies in the pediatric population; it is necessary to characterize the microbiome profile in hypertensive and obese hypertensive children compared to their siblings and their healthy counterparts.

Understanding the nature of hypertension-related microbial aberrations in various body sites, may enable future development of personalized microbiome-based diagnostics and therapies for individuals at risk. Identifying specific microbial signatures associated with the high-risk population may potentially serve as a biomarker to develop non-invasive diagnostics tools. Multiple promising interventions have been described to restore a more balanced microbiome; such treatments need to be further examined in a systematic way to evaluate their potential in lowering blood pressure through modulation of the microbiota. It is worth mentioning that clinical trial NCT02188381 is currently recruiting participants to study gut microbiota involvement in the neuroinflammation-mediated initiation and establishment of resistant hypertension, as well as the possible beneficial role of minocycline therapy on outcomes in resistant hypertension.

Large, prospective clinical trials to establish a more definitive relationship between dysbiosis and high blood pressure and to identify specific microbial signatures in hypertensive subjects are needed before deploying any therapies targeted at altering the microbiota composition.

## AUTHOR CONTRIBUTIONS

All authors (IS, BR, and SA) have equally contributed to the manuscript.

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