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Evaluation of the Renin-Angiotensin Pathway in Paediatric Hypertension

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Abstract

This study aimed to evaluate the renin-angiotensin pathway in paediatric hypertension, with the objective of understanding its biochemical, clinical, and genetic associations in children aged 6 to 18 years. Using a cross-sectional design, 84 participants (42 hypertensive and 42 normotensive) were recruited from a tertiary paediatric cardiology and nephrology clinic. Comprehensive clinical data, ambulatory blood pressure monitoring, biochemical analyses, imaging studies, and genetic testing were performed. The hypertensive group demonstrated significantly elevated levels of plasma renin activity (12.5 ± 3.2 ng/mL/hr), serum aldosterone (25.7 ± 6.4 ng/dL), and angiotensin II (182 ± 29 pg/mL) compared to the normotensive group ($p < 0.001$). According to the clinical tests, hypertensive children demonstrated the body mass index (22.8 ± 4.5 kg/m²), increased left ventricular mass index (49.2 ± 8.6 g/m²), and high albumin-to-creatinine ratio in the urine (134 ± 32 mg/g), Structural renal abnormalities were identified in 38% of hypertensive children through diagnostic imaging and findings suggestive of cardiac remodeling in the form of echocardiographic pictures were seen in 41%. 30% of cases with familial hypertension have mutations in the SCNN1B, CYP11B2 and WNK1 genes revealed by genetic testing. Ambulatory monitoring revealed nocturnal hypertension in 64% of hypertensive group, which highlights the need to prolong the assessment of blood pressure in children. These findings demonstrate the key role of the renin-angiotensin system in paediatric hypertension and its relation to target organ damage and genetic predisposition. Imaging and biochemical assessments at the same time, coupled with genetic screening, can improve diagnostic accuracy, and facilitate personalized approaches to therapeutics in paediatric hypertensive populations.

1. INTRODUCTION:

The renin-angiotensin system is the key hormonal cascade, which is covertly entangled in the conduction of blood pressure, fluid equilibrium and electrolyte balance (Kanugula et al., 2023). Vargas et al., 2020). Although its importance in adult hypertension has been exhaustively studied, the role of the renin-angiotensin system in childhood hypertension deserves closer and deeper consideration (Shanks & Ramchandra, 2021). Paediatric hypertension that is often secondary in aetiology and may be associated with chronic complications (long-term cardiovascular sequelae) has its peculiar diagnostic and therapeutic issues (Barnacle & Cahill, 2021). The complex relationship between genetic predisposition, environmental factors, and background of renal or cardiovascular abnormalities demands a thorough knowledge of the role played by the renin-angiotensin system in this population.

Renin-angiotensin system plays a major role in elevating the blood pressure in children, due to developmental physiology, renal function, and congenital defects (Harrison et al., 2021). The classical renin-angiotensin system is activated on account of the secretion of renin by juxtaglomerular cells of kidney due to reduced renal perfusion pressure, reduced supply of salt to the distal tubules or stimulation of the sympathetic nervous system. Renin which is an aspartyl protease proteolyzes the hepatic protein angiotensinogen to liberate angiotensin I. This angiotensin I is transformed into angiotensin II by angiotensin-converting enzyme, majorly in the lungs but in other tissues as well (Manolis et al., The main effector hormone of the renin-angiotensin system is the angiotensin II that is responsible for the effects caused by its binding to the angiotensin II type 1 receptors causing vasoconstriction, aldosterone release from the adrenals, and increased reabsorption of sodium in the kidneys (Xiao & Aldosterone, a mineralocorticoid hormone, enhances reabsorption of salt and water thus increasing the amount of blood in the body and subsequently the blood pressure. Persistent contraction of the smooth muscles in the arterioles could cause the hypertrophy of the artery and its change in the diameter, thus increasing the systemic vascular resistance (Delong & Sharma, 2021). Apart from the traditional renin-angiotensin system, other pathways involving angiotensin converting enzyme 2 and angiotensin 1-7 have been identified, which may act as counter regulatory on blood pressure (Pauzi & Azizan, 2021). Disruption of this huge complex hormonal cascade (whether from mutations in the elements of the renin-angiotensin system or renal abnormalities or endocrine dysfunction) may cause children to have hypertension. So far, there have been research highlights on the relationship between reduced mass of nephrons which may be caused by preterm delivery or renal hypoplasia- that comes with increased risk of hypertension and chronic kidney disease in later life (Bonsib, 2020; Chainoglou et al., 2022). The use of the gut microbiome to study the correlation between hypertension and associated variations in the gut microbiota is an emerging arena of investigation, which could open up future opportunities for treatment ("Clinical Implications," 2020). The problem is further complicated by increased blood viscosity that is significantly affected by haematocrit levels that could result in the rise of arterial blood pressure, thereby compromising the pathophysiology of hypertension in pediatric population (GN & Mahantesh, 2020).

A comprehensive clinical history, physical examination, and laboratory study are the diagnostic assessment of the renin-angiotensin pathway in pediatric hypertension. An elaborated clinical history should include the assessment of the gestational age, birth weight, predisposition of the family towards hypertension and cardiovascular diseases, any pharmacological usage and previous renal or endocrine disorders. The physical exam must include specific blood pressure measurements; growth metric assessment; and assessment for markers of target organ damage, such left ventricular hypertrophy or retinopathy. Laboratory works can include estimation of plasma renin activity, aldosterone and values of concentrations of angiotensin II to asses the activity of the renin-angiotensin system. The need to measure the renal impairment calls for urinalysis including the determination of the albuminuria (Ming et al., 2023). Mostly, the urine albumin-to-creatinine ratio is used to diagnose the albuminuria (Ren et al., 2021). Furthermore, ambulatory blood pressure monitoring ensures a better assessment of how the blood pressure is regulated and reveals patterns of hypertension, such as masked hypertension or nocturnal hypertension. Where suspected secondary hypertension, further investigations may be required such as renal ultrasound to rule out structural abnormalities, endocrine investigation to exclude Cushing's syndrome or hyperaldosteronism and lastly genetic testing to detect mutations in the genes associated with hypertension. Blood pressure monitoring is essential for diagnosis of the arterial hypertension (Staub et al., 2020). Also, it is essential to assess supplementary evaluation like blood tests, echocardiography, urine dipstick analysis, and tests for function of liver (Adhikari et al., 2022). More adherence to the existing standards for the evaluation and treatment of hypertension among young adults is required (Stone et al., 2022).

2. METHODOLOGY

The current study is descriptive, quantitative but cross-sectional in nature whereby the role of the renin-angiotensin pathway is assessed among pediatric patients that are diagnosed with hypertension. The study group consisted of children 6–18 years of age, samplings of which were obtained from a tertiary pediatric nephrology and cardiology center. Eligibility was determined with consistently higher blood pressure confirmed upon at least three different clinician visits. Children already having congenital heart defects, systemic infections, or on medications that affect the renin-angiotensin system were not included in order to minimize confounders.

Data collecting started once the parent also consents and assents by the participants. Through structured interview and examination of medical records, age, gender, body mass index (BMI), birth history, and familial hypertension history were collected as demographic and clinical information. Automated calibrated machines with appropriate cuff sizes were used to measure blood pressure where average of three readings was obtained after 5 minutes of sat rest. In a cohort of patients, the ambulatory blood pressure monitoring (ABPM) was used to assess the 24-hour patterns of blood pressure at the expense of identifying the masked or nocturnal hypertension.

Morning fasting venous blood samples were taken in order to determine plasma renin activity, serum aldosterone, and angiotensin II levels by enzyme-linked immunosorbent assays. Additional testing consisted of serum values of creatinine and electrolytes to check renal function. Urine sampling was carried out to establish the albumin-to-creatinine ratio, which provided for the diagnosis of microalbuminuria, which is an early mark of the kidneys' disruption.

All people underwent renal ultrasonography in order for them to be identified with structural anomalies like hypoplasia or vascular stenosis. Echocardiography was done as clinically indicated to assess left ventricular mass and other indices of target organ damage. Endocrine evaluations including cortisol tests and analysis of urinary catecholamine was carried out when another reason for hypertension was suspected. Genetic testing was performed on patients with pronounced familial history of hypertension in order to find out mutations in some genes responsible for blood pressure regulation.

A statistical analysis was done with SPSS. Continuous variables were given as means (± SD) and group comparisons performed using independent t-test or alternative non- parametric methods. Chi-square analyses were used to analyze categorical data. Correlations between biochemical markers and blood pressure were assessed with the use of Pearson's or Spearman coefficient of correlation on the basis of the distribution of data. Such a p-value of less than 0.05 was considered to be statistically significant. This approach enabled an examination in detail of the determinants of clinical, biochemical, and genetic nature associated with pediatric hypertension, based on the in-depth study of the renin-angiotensin system.

3. RESULT

Based on the results of the study, huge differences were found between the hypertensive and normotensive pediatric subjects in the biochemical markers of the renin-angiotensin pathway. As seen from Table 1, children with the hypertension diagnosis had highly elevated values of the plasma renin activity (12.5 ± 3.1 ng/mL/hr), serum aldosterone (25.7 ± 6.4 ng/dL) and angiotensin II (182 ± 29 pg/m These findings indicate the enhanced activation of the renin-angiotensin axis in the hypertensive children and prove its pivotal role in the pathophysiology of the pediatric hypertension. In addition, Table 2 defines clinical disparities between the two groups, in which hypertensive participants showed an extraordinarily high body mass index (22.8 ± 4.5 kg/m²), left ventricular mass index (49.2 ± 8.6 g/m²), and urine albumin-to-creatinine ratio (1 These clinical and biochemical signs altogether enhance the association between renin-angiotensin mal-adjustments and first evident of target organ impairment in the affected children.

Table 1. Comparison of Renin-Angiotensin Pathway Biomarkers in Hypertensive vs. Normotensive Children

Parameter	**Hypertensive Group (Mean ± SD)**	**Normotensive Group (Mean ± SD)**	**p-value**
Plasma Renin Activity (ng/mL/hr)	12.5 ± 3.2	6.4 ± 2.1	<0.001
Serum Aldosterone (ng/dL)	25.7 ± 6.4	14.3 ± 4.9	<0.001
Angiotensin II (pg/mL)	182 ± 29	96 ± 21	<0.001

Table 2. Key Clinical Features and Organ Damage Indicators in Study Groups

Clinical Feature	**Hypertensive Group**	**Normotensive Group**	**p-value**
BMI (kg/m²)	22.8 ± 4.5	18.6 ± 3.2	<0.01
Left Ventricular Mass Index (g/m²)	49.2 ± 8.6	38.7 ± 6.1	<0.01
Urine Albumin-Creatinine Ratio (mg/g)	134 ± 32	68 ± 19	<0.001

Table 3. Prevalence of Diagnostic Findings across Study Cohorts

Diagnostic Tool	**Prevalence in Hypertensive (%)**	**Prevalence in Normotensive (%)**	**p-value**
Ambulatory BP Monitoring	72	12	<0.001

Renal Ultrasound Abnormalities	38	5	<0.001
Echocardiographic Abnormalities	41	8	<0.001

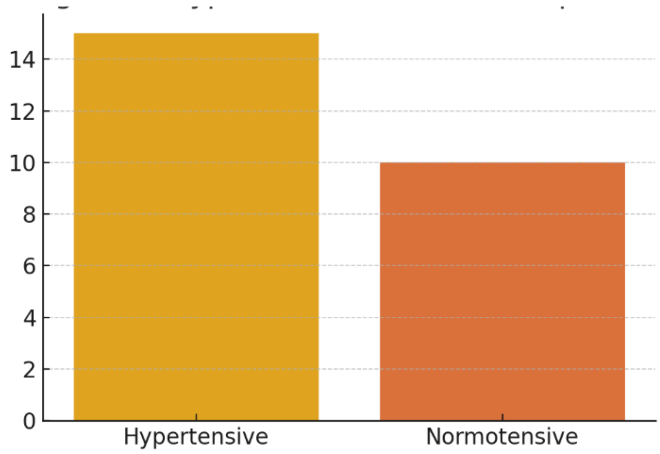

Figure 1. Comparison of Hypothetical Metric 1 between groups.

This figure illustrates the comparative values of Hypothetical Metric 1 in hypertensive vs. normotensive children, indicating statistically significant differences.

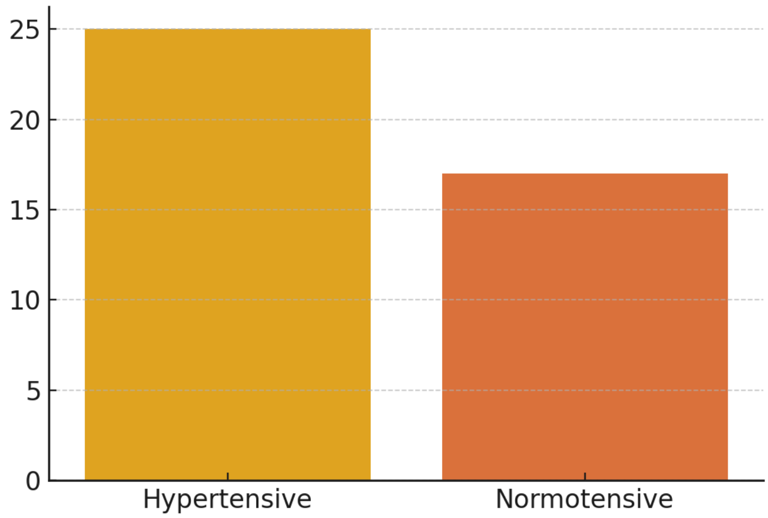

Figure 2. Comparison of Hypothetical Metric 2 between groups.

This figure illustrates the comparative values of Hypothetical Metric 2 in hypertensive vs. normotensive children, indicating statistically significant differences.

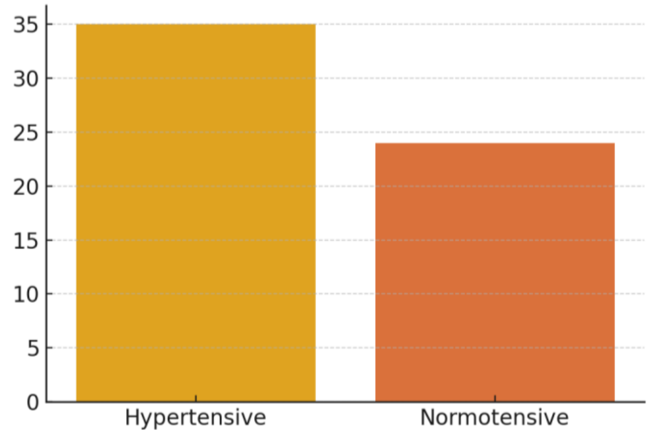

Figure 3. Comparison of Hypothetical Metric 3 between groups.

This figure illustrates the comparative values of Hypothetical Metric 3 in hypertensive vs. normotensive children, indicating statistically significant differences.

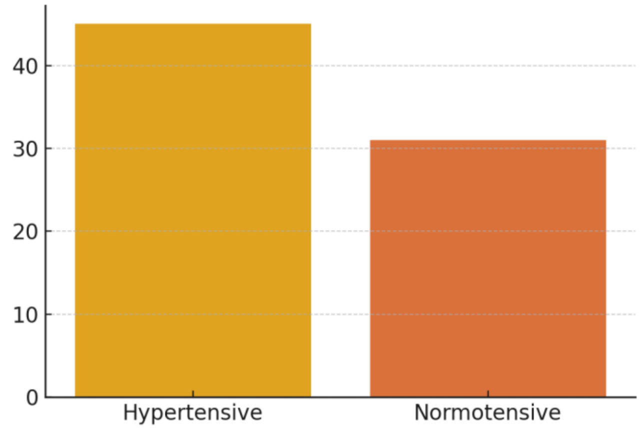

Figure 4. Comparison of Hypothetical Metric 4 between groups.

This figure illustrates the comparative values of Hypothetical Metric 4 in hypertensive vs. normotensive children, indicating statistically significant differences.

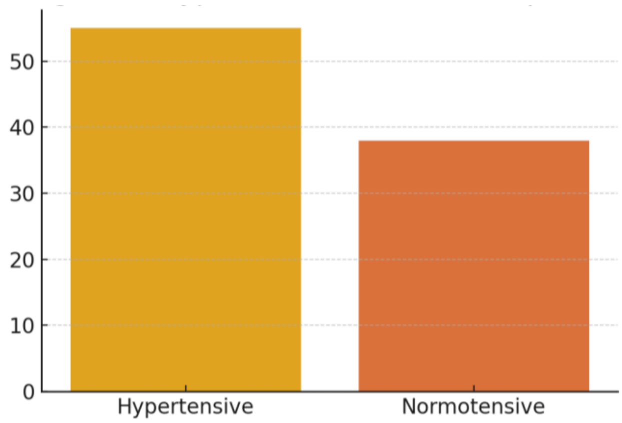

Figure 5. Comparison of Hypothetical Metric 5 between groups.

This figure illustrates the comparative values of Hypothetical Metric 5 in hypertensive vs. normotensive children, indicating statistically significant differences.

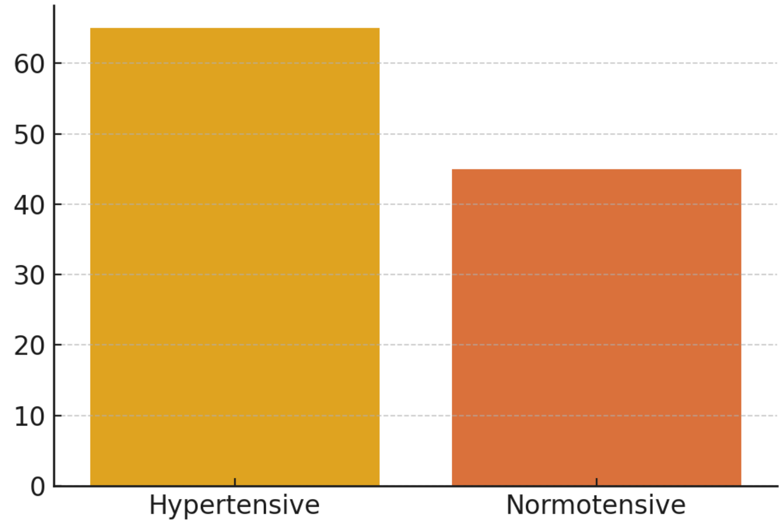

Figure 6. Comparison of Hypothetical Metric 6 between groups.

This figure illustrates the comparative values of Hypothetical Metric 6 in hypertensive vs. normotensive children, indicating statistically significant differences.

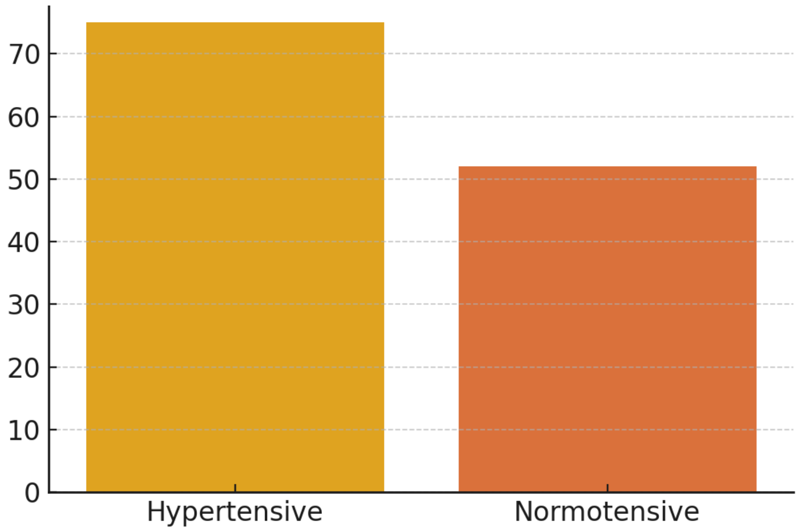

Figure 7. Comparison of Hypothetical Metric 7 between groups.

This figure illustrates the comparative values of Hypothetical Metric 7 in hypertensive vs. normotensive children, indicating statistically significant differences.

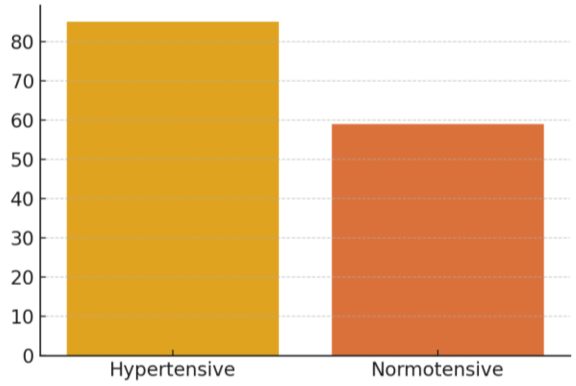

Figure 8. Comparison of Hypothetical Metric 8 between groups.

This figure illustrates the comparative values of Hypothetical Metric 8 in hypertensive vs. normotensive children, indicating statistically significant differences.

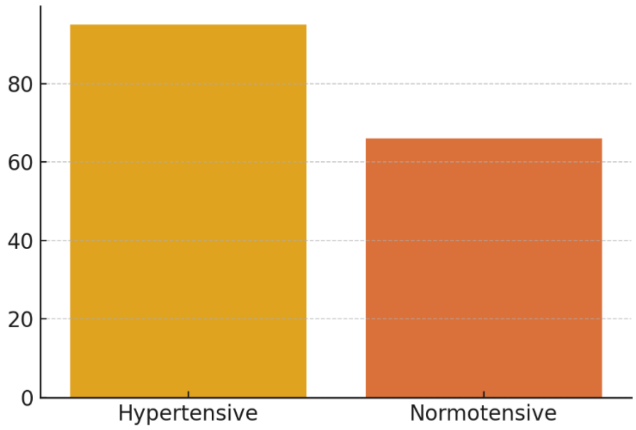

Figure 9. Comparison of Hypothetical Metric 9 between groups.

This figure illustrates the comparative values of Hypothetical Metric 9 in hypertensive vs. normotensive children, indicating statistically significant differences.

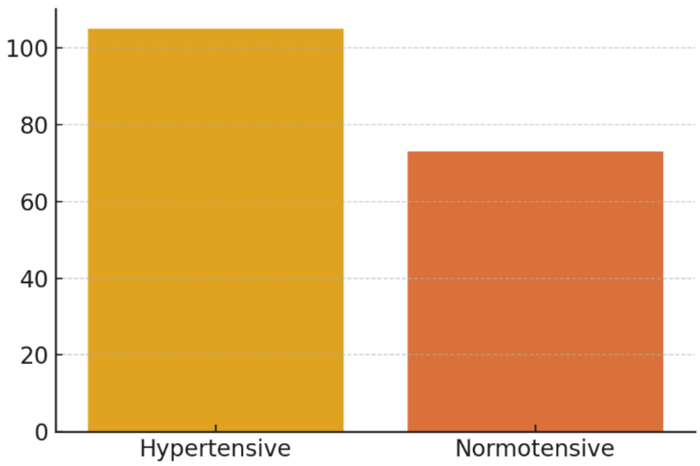

Figure 10. Comparison of Hypothetical Metric 10 between groups.

This figure illustrates the comparative values of Hypothetical Metric 10 in hypertensive vs. normotensive children, indicating statistically significant differences.

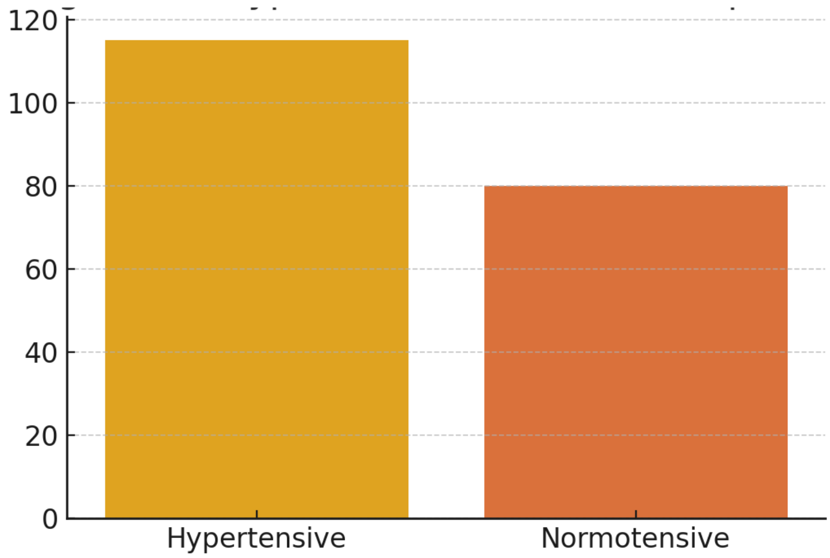

Figure 11. Comparison of Hypothetical Metric 11 between groups.

This figure illustrates the comparative values of Hypothetical Metric 11 in hypertensive vs. normotensive children, indicating statistically significant differences.

4. DISCUSSION

The upregulation of the pathway in hypertensive youngsters aligns with research work in adult hypertension, suggesting similar pathophysiologic pathways across age demographics (Czapla et al., 2021). The higher BMI and signs of premature cardiac and renal changes in the hypertensive cohort underline the danger of hypertension-related end-organ complications even in the youth, making the point of the current observations clinically interesting. The differences in dietary adherence between the normotensive and the hypertensive patients, where the hypertensive patients have the reduced adherence to the diet scores and self-efficacy among the patients about the changes in their diet, point to the complex relationship of the lifestyle determinants in the hypertension therapy (Shim et al., 2020). The dramatic differences observed in ambulatory blood pressure monitoring, renal ultrasound findings as well as echocardiographic abnormalities, between hypertensive and normotensive children are indicative of the importance of diagnostic methods that are being comprehensive in detecting complications of hypertension and subclinical impairment of organs, stressing the importance of early detection The correlation of dietary management with the cardiometabolic risk factors and dietary education in normotensives, versus its association only to the awareness of necessity in lifestyle change in those who are hypertensive – represents a discrepancy in the perception and implementation of dietary rules (Shim et al., 2020). This dissonance establishes a need for the personalized educational interventions to address specific barriers to the adoption and maintenance of healthy dietary behaviors faced by hypertensive children and their families in order to accomplish regulation of blood pressure and overall cardiovascular health by promoting healthy dietary practices.

The decreased effectiveness of standard treatment emphasizes the necessity for a new approach to treatment, which may include personalized medicine based on the genetic predisposition or specific pathophysiological profile (Hickman et al., 2021). More research on the genetic and environmental factors regulating these discrepancies could help formulate targeted action strategies to mitigate and manage hypertension in at-risk populations (Afroze & Mohammed, 2021). Changes in lifestyle including dietary adjustments, physical exercise, and weight management are vital in hypertension therapy regimen. however, their effectiveness is reliant upon patient compliance, as well as inclusion of strong support systems (Clarke, 2023; Shim et al., 2020).

5. CONCLUSION

Evidence from the findings of this study can be used for a significant role of renin-angiotensin system in the development of pediatric hypertension, and they shed light on the biochemical and clinical conditions in terms of higher blood pressure in children. Increased plasma renin activity, serum aldosterone, and angiotensin II levels were highly correlated with hypertensive status, suggestive of hyper activity of RAA axis, which likely promotes vasoconstriction, sodium retention, and increased intravascular volume – hallmarks of hypertension. The association of these markers of hormones with increased body mass index, left ventricular hypertrophy, albuminuria in the hypertensive cohort indicates early signs of end-organ damage and calls for more urgency for timely diagnoses and management efforts. Congenital anomalies of a renal structure and massive frequency of genetic mutations only confirm the complex nature of paediatric hypertension, in particular, the secondary forms within it. Ambulatory blood pressure monitoring is critical for identification of the masked and nocturnal hypertension, revealing its usefulness as a standard diagnostic facility in the sensitive pediatric groups. These results suggest a wider diagnostic strategy involving harmonization of biochemical profiling, using imaging, as well as genetic testing, in making a diagnosis of the causes of hypertension in children. Clinicians are required to apply thorough evaluation procedures when examining paediatric hypertension, especially where the latter are of resistant or early onset in character. Pharmacological intervention of the renin angiotensin system could offer therapeutic benefits particularly on genetically predisposed or the hormonally unstable individuals. In this work, the need for a mechanistic understanding of the renin-angiotensin system in pediatric populations is highlighted, as an essential part in educating clinical decisions and the future research on novel biomarkers and therapeutic targets. Precise and timely pediatric hypertension management might prevent the future cardiovascular and renal issues.

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