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Blood Pressure and Visit-to-Visit Blood Pressure Variability among Individuals with Primary Proteinuric Glomerulopathies

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Abstract

Hypertension and blood pressure variability (standard deviation and average real variability) in primary proteinuric glomerulopathies are not well described. Data were from 433 participants in the Nephrotic Syndrome Study Network (NEPTUNE). Hypertensive blood pressure status was defined as prior history of hypertension or blood pressure ≥140/90 mmHg for adults/≥95th% for children at baseline. Blood pressure variability was measured in participants with ≥3 visits in the first year. 296 adults (43 [IQR 32,57.8] years, 61.5% male) and 147 children (11 [IQR 5,14] years, 57.8% male) were evaluated. At baseline, 64.8% of adults and 46.9% of children were hypertensive. Histologic diagnosis was associated with hypertensive status in adults ($p = 0.036$). In adults, hypertensive status was associated with lower hazard of complete remission (HR 0.36, 95%CI 0.19,0.68) and greater hazard of achieving the composite endpoint (ESRD or eGFR decline >40%; HR 4.1, 95%CI 1.4,12). Greater systolic and diastolic standard deviation and average real variability were also associated with greater hazard of reaching the composite endpoint in adults (all $p<0.01$). In children, greater blood pressure variability was an independent predictor of composite endpoint (determined by systolic standard deviation and average real variability) and complete remission (determined by systolic and diastolic average real variability) (all $p<0.05$). Hypertensive status was common among adults and children enrolled in NEPTUNE. Differences in hypertensive status prevalence, blood pressure variability and treatment were found by age and

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Disclosures

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histologic diagnosis. In addition, hypertensive status and greater blood pressure variability were associated with poorer clinical outcomes.

Keywords

hypertension; nephrotic syndrome; minimal change disease; FSGS; membranous nephropathy; pediatric; NEPTUNE

Introduction

Nephrotic syndrome is recognized as a significant cardiovascular disease (CVD) risk factor, associated with hypertension and accelerated atherosclerosis. In fact, the American Heart Association classifies nephrotic syndrome in children as a Tier II CVD risk factor [1]. Primary glomerular diseases such as membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) often become manifest in individuals when nephrotic syndrome develops, and treatment focuses on decreasing proteinuria and inducing remission. The clinical course of these diseases can include periods of remission and relapse of nephrotic syndrome. Hypertension and CVD are co-morbid conditions associated with these entities.

While not completely understood, there are several possible pathophysiologic mechanisms for the development of elevated blood pressure (BP) and hypertension among individuals with primary proteinuric glomerulopathies. Proposed etiologies include renin-angiotensin aldosterone system (RAAS) activation, sodium retention and volume expansion either due to RAAS activation or secondary to a sodium-handling defect [2]. Elevated BP is also due to medication side effects of corticosteroids and calcineurin inhibitors (CNI) that are commonly used in the treatment of individuals with proteinuric disease. Despite the increased risk for CVD morbidity and mortality among these individuals, the prevalence of hypertension, anti-hypertensive treatment patterns and relationship of hypertension to clinical outcomes in these specific glomerular diseases have not been well described.

Independent of adequate BP control, visit-to-visit BP variability (BPV), defined as the degree of variation between discrete BP readings at separate time points, has been shown to predict cardiovascular morbidity and mortality in the general population and in patients with chronic kidney disease [3–6]. Additionally, greater visit-to-visit BPV has been associated with worse proteinuria and renal function [7,8]. The relationship between visit-to-visit BPV and renal outcomes in proteinuric glomerular disease is unknown.

To characterize CVD risk factors and anti-hypertensive treatment patterns among a contemporary cohort of adults and children with primary glomerular diseases that can present with nephrotic syndrome, we studied individuals enrolled in the Nephrotic Syndrome Study Network (NEPTUNE). The goals of this study were: i) to define the prevalence and management of hypertensive BP status in patients with primary proteinuric glomerulopathies across age groups and histologic diagnoses; ii) to determine if hypertensive BP status and BPV were associated with adverse renal outcomes.

Materials and Methods

Nephrotic Syndrome Study Network (NEPTUNE)

The design of the NEPTUNE study has been previously described in detail [9]. Briefly, NEPTUNE is a multi-center observational cohort study of children and adults with glomerular diseases that cause nephrotic syndrome. Participants of any age with ≥500 mg/day of proteinuria on a 24-hour urine sample or with a urine protein/creatinine ratio (UPC) ≥0.5 g/g on a spot urine specimen were enrolled at the time of a clinically indicated kidney biopsy at 21 sites in North America. Patients with kidney manifestations of systemic disease, prior solid organ transplant or life expectancy <6 months were excluded. There were 470 participants enrolled between July 1, 2010 and May 1, 2016. Participants were assigned to the following disease cohorts based on histologic confirmation by core pathologists: MCD, FSGS, MN or other glomerulopathy, which included IgA nephropathy (IgA) [10]. Study visits consisted of data and biosample collection at baseline, every 4 months during the first year and then every 6 months for a total of 5 years. The study protocol was approved by the Institutional Review Board at each participating site and informed consent/assent was obtained from each participant.

Blood Pressure Measurements

Casual BP measurements were obtained in triplicate at each study visit using a calibrated oscillometric device. BP was measured in the right arm with the participant in a seated position after five minutes of rest. The average of the last two readings was used. Participants were classified as “Hypertensive BP Status” (HTN) if either of the following criteria were met: 1) a clinical diagnosis of hypertension was recorded in their medical record or 2) their average baseline BP was in the hypertensive range for age. Among the subset of individuals categorized as HTN who had a prior clinical diagnosis of hypertension, those with an average baseline BP either ≥95th percentile for age, sex and height [11] for children or ≥140 mmHg systolic or ≥90 mmHg diastolic [12] for adults, were consider to be “Hypertensive Uncontrolled”. Those with a clinical diagnosis of hypertension with BPs below these thresholds were considered “Hypertensive Controlled”. To allow for comparison across adults and children, a systolic and diastolic BP index was calculated: average measured BP was divided by 140 or 90 as applicable in adults or by the sex, age and height specific 95th percentile BP in children. Although BP index has not been used previously in adult studies, BP index is a common approach to standardize BP among individuals of different age, sex and size in the pediatric literature [13–15]. BP index ≥1 indicates BP in the hypertensive range and every 0.1 unit increase represents a 10% increase in BP above hypertensive range.

Visit-to-visit BPV was calculated using BP measurements obtained during the first year of the study in participants with ≥ 3 separate visits with a documented BP measurement. We chose to examine two metrics of systolic and diastolic BPV: 1) standard deviation (SD) which measures overall variability and 2) average real variability (ARV) which measures variability between consecutive visits and was calculated as the mean difference in BP between visits [16].

Cardiovascular Disease Risk Factors, Covariate and Outcome Measurements

Clinical and demographic characteristics including immunosuppressive and anti-hypertensive medication use, UPC, serum creatinine and self-reported smoking status were collected from the participants. Children <18 years old were categorized into the pediatric group; all others were categorized as adults. Weight status was classified into normal, overweight and obese categories based on reference data for body mass index (BMI) in adults or BMI percentile in children [17]. The presence of edema was documented by a clinician at each study visit. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-Epi formula for participants ≥18 years and the modified Schwartz formula for participants <18 years [18,19].

Renal outcomes that were pre-determined by NEPTUNE included Complete Remission Ever, Composite Endpoint and eGFR slope. Complete Remission Ever was defined as UPC ≤0.3 at any study visit. The Composite Endpoint was defined as development of End Stage Renal Disease (ESRD) or eGFR decline by ≥40% by the time of the last follow up. The eGFR slope of the least-squares regression line was calculated for each person using the first and last serum creatinine measured at least 8 months apart, reported as mL/min/year.

Statistical Analysis

NEPTUNE participants with BP recorded at the baseline visit were included in this analysis. Adult and pediatric patients were considered separately and then compared. Descriptive statistics were used to describe the demographic and clinical characteristics among the full cohort, stratified by age and histologic subgroups based on chi-square/Fisher's exact tests or the Wilcoxon Rank Sum/Kruskall Wallis test for categorical and continuous variables, respectively. Multivariable logistic regression was used to evaluate the association of disease cohort and odds of having HTN for both adults and children adjusting for age, sex, race, weight status (overweight/obese vs. not), edema (yes/no), steroid use (yes/no), CNI use (yes/no), eGFR, and smoking status (yes/no; adults only).

To evaluate the association of renal outcomes (eGFR slope, Composite Endpoint and Complete Remission Ever) with HTN and BPV, regression models were used adjusting for age, sex, race, disease cohort, and follow up time (Model 1). A second model (Model 2) included those variables from Model 1 in addition to smoking status, CNI/steroid use, RAAS use, weight status, edema, cholesterol, and baseline SBP index and baseline eGFR. Multiple linear regression based on generalized estimating equations to account for the correlation of individual-level clinical visits was used to determine the relationship between HTN and BPV with eGFR slope. Finally, pooled logistic regression models with a complementary log-log link was used to evaluate the association of HTN and BPV with time to Complete Remission Ever and the Composite Endpoint. Results of these analyses are presented as hazard ratios (HR) with corresponding 95% CI. The time to event analysis started with the baseline visit. The entire follow up period was used to analyze outcomes where HTN was the primary exposure of interest, while a minimum of two visits after year 1 in participants were included in the outcome analysis for BPV only. All analyses were conducted using SPSS, version 24 (IBM Inc.) and R version 3.3.2[20]. A two-sided p-value of 0.05 or less was considered statistically significant.

Results

Patient Population

There were 443 participants with baseline blood pressure, including 296 adults and 147 children enrolled in NEPTUNE as of May 1, 2016. Cross-sectional baseline demographic and clinical characteristics of the study cohort stratified by age group are summarized in Table 1. There was a significantly greater proportion of black race and lower prevalence of obese/overweight in the pediatric group. Diagnosis differed by age group; there was a higher proportion of MN in adults and a higher proportion of MCD in children. Children had a significantly higher eGFR and lower UPC than adults. The pediatric group also had a significantly greater proportion of participants treated with steroids and CNI than the adult group. For the entire cohort, the median follow-up time was 24 (IQR 12, 37) months with a median of 4 (IQR 2, 7) visits (13.8% with 3 visits, 11% with 4 visits, 10% with 5 visits, 9.6% with 6 visits and 27.9% with ≥ 7 visits). There was no difference in mean follow up time between age groups.

Hypertensive BP Status

At baseline, 261 participants (58.9%) had a previous clinical diagnosis of hypertension (N = 207) or had baseline BP in the hypertensive range (N = 54), and were classified as HTN. Children were disproportionately more likely to be categorized as HTN based on baseline BP than by previous clinical diagnosis of hypertension, 59.4% (N = 41/69) vs 40.6% (N = 28/69), p= 0.001, respectively. While HTN was more prevalent among adults than children, children were more likely to be categorized as hypertensive uncontrolled (Table 1).

Comparing by disease cohort, there was a significant difference in prevalence of HTN across the disease groups in adults but not in children (Table 2). Disease cohort was significantly associated with HTN after adjustment for age, sex, race, weight status, edema, steroids, CNI, eGFR and smoking (adults) in adults (p = 0.036) but not in children (p = 0.9). For adults, the odds of HTN were 5.5 times greater in IgA and 3.8 times greater in FSGS compared to MCD (Table 3).

Treatment Patterns

Anti-hypertensive treatment by age group is shown in Supplementary Table S1. In contrast to adults, children more frequently were not treated with anti-hypertensive medications (43.5% vs. 12.1%) at baseline (p <0.001). Overall, RAAS blockade (65.1%) was most common followed by diuretics (35.7%) and calcium channel blockers (22.2%). A greater proportion of adults were taking each class of anti-hypertensive medication as compared to children (all p < 0.05).

Blood Pressure Variability

There were 378 (85.3%) participants with ≥3 BP readings over separate visits during the first year of participation in NEPTUNE from which visit-to-visit BPV was calculated. Adults had significantly greater systolic SD and ARV compared to children (Table 1). There was no significant difference in these parameters by disease cohort (Table 2).

Variables were assessed in regression models to examine determinants of BPV in adults and children. In adults, black race (β = 2.8, 95% CI 0.65, 4.9, p = 0.01) and baseline systolic BP (β = 0.08, 95% CI 0.03, 0.13, p = 0.004) were significantly associated with systolic SD in the multivariable model adjusting for age, sex, race, weight status and edema. Black race was also associated with systolic ARV in adults (β = 3.6, 95% CI 0.67, 6.6, p = 0.02). In children, baseline systolic BP was a directly related to systolic SD (β = 0.23, 95% CI 0.15, 0.3, p < 0.0001) and systolic ARV (β = 0.2, 95% CI 0.12, 0.3, p < 0.0001). Disease cohort, anti-hypertensive medication class, immunosuppression, weight status and edema were not associated with BPV in adults or children.

Hypertensive BP Status and BPV with Outcomes

Overall, after a median of two years of follow up there were 212 Complete Remission Ever events (129/296 in adults and 83/147 in children) and 91 Composite Endpoint events (69/296 in adults and 22/147 in children).

In adults, HTN was significantly associated with a lower hazard of Complete Remission Ever (p<0.001) in Models 1 and 2 (Table 4 and Supplementary Figure S1). HTN was also associated with a 4.1 times greater hazard of reaching the Composite Endpoint only in the more parsimonious Model 1 (Figure 1). There was no association of baseline HTN with eGFR slope. Greater systolic and diastolic BPV were associated with a greater hazard of reaching the Composite Endpoint (Table 4). For each one unit increase in systolic SD there was a 5% increase in the occurrence of the Composite Endpoint (Model 1). For systolic ARV there was a 10% increase in Composite Endpoint for each one unit increase (Model 1).

In children, HTN trended towards lower hazard of Complete Remission Ever in Model 1, but failed to reach statistical significance (Table 5). HTN was not associated with eGFR slope or Composite Endpoint in children. Greater systolic SD and ARV were associated with a greater hazard of reaching the Composite Endpoint in Model 1. Systolic and diastolic ARV were also associated with a lower hazard of Complete Remission Ever in children (Table 5).

Discussion

In this large cohort of adults and children with primary proteinuric glomerulopathies, nearly 60% of participants had HTN at enrollment. Although HTN was more prevalent among adults, children were more often categorized as having uncontrolled BP. Treatment with anti-hypertensive medication was common, although less so in children compared to adults. Of the various antihypertensive classes, RAAS blockade was the most commonly prescribed, with two-thirds of the population overall treated with these agents. In adults, HTN was associated with lower odds of Complete Remission Ever and greater hazard of reaching the Composite Endpoint of ESRD or eGFR decline by ≥40%. Adults had significantly greater BPV as determined by systolic SD and ARV when compared to children, and these measures, along with diastolic SD and ARV, were associated with a greater hazard of reaching the Composite Endpoint in adults. In children, BPV was also associated with greater hazard of reaching the Composite Endpoint (as determined by systolic SD and ARV) and with a lower hazard of reaching Complete Remission Ever (as determined by systolic and diastolic ARV).

Although nephrotic syndrome is known to be associated with increased cardiovascular risk, there is little known regarding the prevalence of hypertension and anti-hypertensive treatment patterns in adults and children with primary proteinuric glomerulopathies associated with nephrotic syndrome. We found that HTN was more common in adults than in children. In agreement with our findings, a smaller study of individuals with FSGS also described a substantial hypertension prevalence: 76% in adults and 44% in children [21]. In other smaller studies of children, hypertension prior to corticosteroid therapy was reported to be uncommon in MCD but was found in 20–50% of children with FSGS at the time of diagnosis [22,23]. Prevalence rates of hypertension as determined by 24-hour ambulatory blood pressure monitoring (ABPM) vary in the literature, ranging from 14–89% [24–26]. Our finding of a higher prevalence of HTN in adults compared to children could possibly be explained by the higher baseline prevalence of essential hypertension found in the general adult population and lower eGFR in adults compared to children in this cohort. Surprisingly, we found that disease cohort was not associated with HTN in children, whereas FSGS and IgA were determinants of HTN in adults. This finding in children could possibly be explained by the almost universal use of steroid/CNI treatment in children regardless of disease cohort. Additionally, we observed that BP was treated more aggressively in adults than in children. As expected, RAAS blockade was the most used class of anti-hypertensive medications, likely owing its anti-proteinuric effects.

There is also a paucity of data regarding the relationship of hypertension with clinical outcomes in primary proteinuric glomerulopathies. Our findings support our hypothesis that HTN is associated with worse clinical outcomes in adults with proteinuric glomerulopathies. We demonstrate that adult hypertensive BP status is associated both with the development of ESRD and with a decline in eGFR of 40% or more. Data from the Chronic Renal Insufficiency Cohort (CRIC) supports that hypertension is associated with progression of renal disease and ESRD, however the cohort includes various etiologies of kidney disease [27]. The scant reports on primary gomerulopathies are conflicting. Moranne et al. reported that baseline hypertension was not predictive of ESRD in those of primary glomerulonephritis, while Chou et al. showed that baseline hypertension in IgA nephropathy (but not in MN or FSGS) was associated with progression to ESRD [28,29]. Interestingly, Zagury et al. showed that hypertension was associated with increased risk for developing ESRD in children with steroid resistant nephrotic syndrome [23]. While this is in contrast to our findings, where we did not find HTN to be associated with poorer outcomes in children, it should be noted that the paper by Zagury et al. was not an adjusted analyses and was limited to children with steroid resistance.

Blood pressure variability is emerging as an important CVD risk factor, with evidence suggesting that it is associated with clinical outcomes [3–6]. Recent literature suggests that visit-to-visit BPV also has promise in predicting renal outcomes. In the ALLHAT study of 21,245 hypertensive adults, greater visit-to-visit BPV was associated with incident ESRD and ≥50% decline in eGFR independent of mean blood pressure [5]. Yano et al. described the association of long-term visit-to-visit BPV with the development of chronic kidney disease in a large Japanese population [30]. A smaller study also in Japan demonstrated that increased visit-to-visit BPV was associated with albuminuria [7]. In the present study, we provide evidence that this association of BPV to renal outcomes can be extended to primary

glomerulopathy populations throughout the lifespan. Our findings also demonstrate that adults have significantly greater systolic SD and ARV compared to children, which is not surprising given that BPV has been shown to increase with mean BP and age [31]. Interestingly, disease cohort, clinical characteristics (weight and edema) and treatment (anti-hypertensive medication class and immunosuppressive medications) were not associated with BPV in adults or children.

There are limitations to this study that should be taken into consideration. Ideally, "hypertension" is defined by the measurement of elevated BP from at least two (adults) or three (children) separate office visits [11,12]. Guidelines further recommend that auscultation is the preferred method of BP measurement over oscillometry [11]. The use of 24-hour ABPM is also increasingly recommended for the diagnosis of hypertension [32]. In this study we utilized prior medical history and the average of two seated oscillometric BPs from the baseline visit to determine "hypertensive BP status". As a result, our findings may be subject to BP mis-classification. However, if normotensive patients were mis-labeled as HTN, we would expect to find weaker associations of HTN with outcomes. Although available, longitudinal measurements of BP in this cohort were not used to define hypertension due to the confounding of anti-hypertensive medication use over time that could have potentially affected BP. This is particularly relevant for this patient population as many are likely prescribed RAAS blockade for treatment of proteinuria. Secondly, although this study focuses on the association of baseline hypertension and BPV with outcomes, the relationship between blood pressure, proteinuria etiology and renal outcomes may not necessarily be causal, especially given the observational nature of the study. However, the renal outcomes evaluated were restricted to a period after the measurement of BPV. An additional limitation is that treatment with anti-hypertensive medications was not stable throughout the study duration; therefore, greater BPV in these patients could be a reflection of changes in BP control due to medications (i.e. patients with higher BP at study initiation could potentially be those who experienced the greatest fall in BP over time, which in turn affects BPV). It should be noted though, that baseline BP and use of RAAS blockade were adjusted for in the regression models for renal outcomes. Lastly, all the NEPTUNE sites are academic centers where practices of blood pressure management may differ from non-academic institutions, thereby possibly affecting the generalizability of our results.

Perspectives

In summary, HTN is common among the adults and children with primary proteinuric glomerular diseases enrolled in NEPTUNE. There were significant differences in the prevalence of HTN, BPV and treatment by age and disease cohort. HTN and greater BPV were associated with poorer renal outcomes, which may have clinical implications. These observations highlight the importance of further research, including clinical trials, to determine the impact of improved BP control on renal and CVD outcomes among individuals with primary proteinuric glomerular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents, National Heart L, Blood I. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011; 128(Suppl 5):S213–256. [PubMed: 22084329]
2. Ray EC, Rondon-Berrios H, Boyd CR, Kleyman TR. Sodium retention and volume expansion in nephrotic syndrome: implications for hypertension. Adv Chronic Kidney Dis. 2015; 22:179–184. [PubMed: 25908466]
3. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet. 2010; 375:895–905. [PubMed: 20226988]
4. Mallamaci F, Minutolo R, Leonardis D, et al. Long-term visit-to-visit office blood pressure variability increases the risk of adverse cardiovascular outcomes in patients with chronic kidney disease. Kidney Int. 2013; 84:381–389. [PubMed: 23615498]
5. Whittle J, Lynch AI, Tanner RM, et al. Visit-to-Visit Variability of BP and CKD Outcomes: Results from the ALLHAT. Clin J Am Soc Nephrol. 2016; 11:471–480. [PubMed: 26912544]
6. Diaz KM, Tanner RM, Falzon L, et al. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. Hypertension. 2014; 64:965–982. [PubMed: 25069669]
7. Kawai T, Ohishi M, Kamide K, et al. The impact of visit-to-visit variability in blood pressure on renal function. Hypertens Res. 2012; 35:239–243. [PubMed: 22011685]
8. Okada T, Matsumoto H, Nagaoka Y, Nakao T. Association of home blood pressure variability with progression of chronic kidney disease. Blood Press Monit. 2012; 17:1–7. [PubMed: 22183043]
9. Gadegbeku CA, Gipson DS, Holzman LB, et al. Design of the Nephrotic Syndrome Study Network (NEPTUNE) to evaluate primary glomerular nephropathy by a multidisciplinary approach. Kidney Int. 2013; 83:749–756. [PubMed: 23325076]
10. Barisoni L, Nast CC, Jennette JC, et al. Digital pathology evaluation in the multicenter Nephrotic Syndrome Study Network (NEPTUNE). Clin J Am Soc Nephrol. 2013; 8:1449–1459. [PubMed: 23393107]
11. National High Blood Pressure Education Program Working Group on High Blood Pressure in C Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004; 114:555–576. [PubMed: 15286277]
12. Armstrong C. Joint National C. JNC8 guidelines for the management of hypertension in adults. Am Fam Physician. 2014; 90:503–504. [PubMed: 25369633]
13. Soergel M, Kirschstein M, Busch C, et al. Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents: a multicenter trial including 1141 subjects. J Pediatr. 1997; 130:178–184. [PubMed: 9042117]
14. Sorof JM, Cardwell G, Franco K, Portman RJ. Ambulatory blood pressure and left ventricular mass index in hypertensive children. Hypertension. 2002; 39:903–908. [PubMed: 11967247]
15. Flynn J, Zhang Y, Solar-Yohay S, Shi V. Clinical and demographic characteristics of children with hypertension. Hypertension. 2012; 60:1047–1054. [PubMed: 22892814]

16. Levitan EB, Kaciroti N, Oparil S, Julius S, Muntner P. Relationships between metrics of visit-to-visit variability of blood pressure. J Hum Hypertens. 2013; 27:589–593. [PubMed: 23535987]
17. Body Mass Index Calculator. 2016. cdc.gov
18. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604–612. [PubMed: 19414839]
19. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009; 20:629–637. [PubMed: 19158356]
20. environment RDCTRAla, for statistical computing. Vienna AR: Foundation for Statistical Computing;
21. Newman WJ, Tisher CC, McCoy RC, et al. Focal glomerular sclerosis: contrasting clinical patterns in children and adults. Medicine (Baltimore). 1976; 55:67–87. [PubMed: 1107746]
22. A report of the International Study of Kidney Disease in Children. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. Kidney Int. 1978; 13:159–165. [PubMed: 713276]
23. Zagury A, Oliveira AL, Montalvao JA, et al. Steroid-resistant idiopathic nephrotic syndrome in children: long-term follow-up and risk factors for end-stage renal disease. J Bras Nefrol. 2013; 35:191–199. [PubMed: 24100738]
24. Xu ZQ, Yi ZW, Dang XQ, Wu XC, He XJ. Relationship of 24-hour ambulatory blood pressure and rennin-angiotensin-aldosterone system in children with primary nephrotic syndrome. Zhongguo Dang Dai Er Ke Za Zhi. 2010; 12:788–792. [PubMed: 20959043]
25. Sarkar S, Sinha A, Lakshmy R, et al. Ambulatory Blood Pressure Monitoring in Frequently Relapsing Nephrotic Syndrome. Indian J Pediatr. 2017; 84:31–35. [PubMed: 27538980]
26. Candan C, Canpolat N, Gokalp S, et al. Subclinical cardiovascular disease and its association with risk factors in children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2014; 29:95–102. [PubMed: 24037224]
27. Grams ME, Yang W, Rebholz CM, et al. Risks of Adverse Events in Advanced CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2017 Mar 30. Epub ahead of print. doi: 10.1053/j.ajkd.2017.01.050
28. Moranne O, Watier L, Rossert J, Stengel B. Group GN-PS. Primary glomerulonephritis: an update on renal survival and determinants of progression. QJM. 2008; 101:215–224. [PubMed: 18245806]
29. Chou YH, Lien YC, Hu FC, et al. Clinical outcomes and predictors for ESRD and mortality in primary GN. Clin J Am Soc Nephrol. 2012; 7:1401–1408. [PubMed: 22798538]
30. Yano Y, Fujimoto S, Kramer H, et al. Long-Term Blood Pressure Variability, New-Onset Diabetes Mellitus, and New-Onset Chronic Kidney Disease in the Japanese General Population. Hypertension. 2015; 66:30–36. [PubMed: 25987664]
31. Mancia, GPG., Di Rienzo, M., Zanchetti, A. Blood pressure variability. In: Zanchetti, A., Mancia, G., editors. Handbook of Hypertension. Amsterdam: The Netherlands: Elsevier; 1997. p. 117-169.
32. Flynn JT, Daniels SR, Hayman LL, et al. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. Hypertension. 2014; 63:1116–1135. [PubMed: 24591341]

Novelty and Significance

What Is New?

- Nephrotic syndrome is recognized as a significant cardiovascular disease risk factor, however, the prevalence of hypertension and blood pressure variability in primary glomerulopathies associated with nephrotic syndrome have not been well described.
- The relationship of blood pressure and blood pressure variability with renal outcomes in primary proteinuric glomerular diseases are not known.

What Is Relevant?

- This study describes hypertension and blood pressure variability in adults and children with primary proteinuric glomerulopathies.

Summary

- In adults and children with primary glomerulopathies associated with nephrotic syndrome, nearly 60% of participants had HTN at enrollment.
- Differences in hypertensive status prevalence, blood pressure variability and treatment were found by age and histologic diagnosis.
- Hypertensive status and greater blood pressure variability were associated with poorer clinical outcomes.

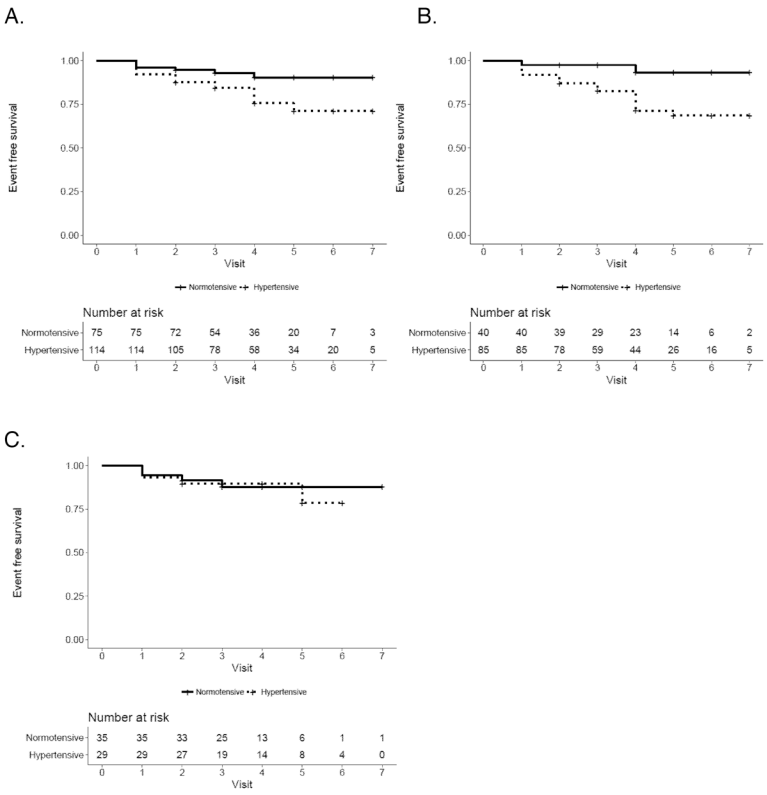

Figure 1.

Kaplan Meier plot of hypertensive blood pressure status and Composite Endpoint (End Stage Renal Disease or glomerular filtration rate decline 40%) **A)** overall (P=0.02) and amongst **B)** adults (P=0.02) and **C)** children (P=0.84)in the NEPTUNE cohort.

Table 1

Demographics and Blood Pressure of the NEPTUNE Cohort at Baseline

Characteristics N (%) or Median (IQR)	Adult N = 296	Pediatric N=147	p-value
Age (years)	43 (32, 57.8)	11 (5, 14)	< 0.0001
Male	182 (61.5%)	85 (57.8%)	0.46
Black	61 (21.3%)	61 (43.9%)	< 0.0001
Hispanic	62 (20.9%)	33 (22.4%)	0.82
BMI (kg/m^2)	28.4 (24.8, 33.2)	20.8 (17.7, 24.9)	< 0.0001
Obese/Overweight	217 (73.3%)	84 (57.1%)	0.003
Edema	133 (44.9%)	55 (37.4%)	0.13
Smoker	31(10.5%)	1(0.7%)	0.001
Disease Duration (months)	12(0,24)	12(0,12)	0.73
Follow Up Time (months)	24.5 (12, 37)	24 (12, 36)	0.49
Cohort: MCD	40 (13.2%)	69 (46.9%)	< 0.0001
MN	71 (24%)	2 (1.4%)	
FSGS	98 (33.1%)	49 (33.3%)	
IgA	48 (16.2%)	8 (5.4%)	
Other *	39 (13.2%)	19 (12.9%)	
Hypertensive BP status †	192 (64.8%)	69 (46.9%)	< 0.0001
Hypertensive Uncontrolled †	69 (23.3%)	61 (41.5%)	<0.0001
SBP (mmHg)	124 (113, 137)	109 (101, 118)	< 0.0001
DBP (mmHg)	77.5 (69, 85)	68 (61, 77)	< 0.0001
SBP Index ‡	0.89 (0.81, 0.98)	0.92 (0.87, 1.0)	< 0.0001
DBP Index ‡	0.86 (0.77, 0.94)	0.90 (0.81, 1.0)	< 0.0001
SBP SD (mmHg)	10 (6.6, 14.7)	7.3(4.5, 10.2)	< 0.0001
DBP SD (mmHg)	6.5 (4.3, 9.7)	7.1 (4.2, 10.7)	0.34
SBP ARV (mmHg)	11.7 (7, 18)	8.0 (5.5, 11.8)	< 0.0001
DBP ARV (mmHg)	8 (5, 11.3)	8 (5.5, 12.2)	0.38
No anti-hypertensive medication	36 (12.1%)	64 (43.5%)	<0.001
1 anti-hypertensive medication	93 (31.4%)	64 (43.5%)	
2 anti-hypertensive medications	101 (34.1%)	15 (10.2%)	
≥3 anti-hypertensive medications	66 (22.2%)	4 (2.7%)	
Steroid use	74 (25%)	102 (69.4%)	< 0.0001
CNI use	9 (3%)	39 (26.5%)	< 0.0001
eGFR (ml/min/1.73m^2)	69.5 (42.6, 96.3)	100.4 (82, 118.3)	< 0.0001
UPC (g/g)	2.3 (0.86, 4.1)	1.2 (0.22, 4.1)	0.005

* Other glomerulopathy cohort included diagnoses of Membranoproliferative Glomerulonephritis, Thin Basement Membrane, C1Q, C3 glomerulopathy, Crescentic Glomerulonephritis, Mesangial, Glomerulosclerosis, Membranous with Nodular Diabetes Mellitus, Nodular Glomerulosclerosis, Thrombotic Microangiopathy, Indeterminate

† Hypertensive BP status defined as prior clinical diagnosis of hypertension or an elevated BP for age at the baseline visit; Hypertensive Uncontrolled defined as prior diagnosis of hypertension and elevated BP at the baseline visit.

‡ BP index- BP was divided by 140 or 90 in adults or by the 95th percentile BP in children; an index ≥1 is indicative of a BP in the hypertensive range

BMI- body mass index; MCD- minimal change disease; MN – membranous nephropathy; FSGS – focal segmental glomerulosclerosis; IgA – IgA nephropathy; BP – blood pressure at baseline; SBP – systolic BP; DBP – diastolic BP; SD – standard deviation; ARV – average real variability; CNI – calcineurin inhibitor; eGFR – estimated glomerular filtration rate; UPC – urine protein:creatinine ratio.

Table 2

Blood Pressure, Blood Pressure Variability and Hypertension Risk Factors by Disease Cohort

Characteristics N (%) or Median (IQR)	Adult				
	MCD N = 40	MN N = 71	FSGS N = 98	IgA N = 48	p-value
Hypertensive BP status *	16 (40%)	46 (64.8%)	73 (74.5%)	34 (70.8%)	0.004
Hypertensive Uncontrolled *	4 (7.1%	9 (16.1%)	26 (46.4%)	10 (17.9%)	0.1
SBP (mmHg)	121 (107.3,129)	121 (113, 135)	125 (115,137.3)	126 (115.3,139.5)	0.33
DBP (mmHg)	74.5 (65, 81.8)	77 (69, 84)	80 (69.8, 88)	78 (73, 85.8)	0.11
SBP SD (mmHg)	7.1(4.9, 12.4)	11.1 (7.1, 16.4)	11 (6.9, 15.8)	8.8 (6.9, 12.2)	0.19
DBP SD (mmHg)	7 (3.4, 8.9)	6.5 (4.2, 9.4)	7.1 (5.2, 9.7)	6.3 (4.3, 10.8)	0.47
SBP ARV(mmHg)	9 (5.3, 17)	13.5 (7.2, 18)	12.8 (8.3, 20.8)	11.2 (7.3, 17.4)	0.52
DBP ARV (mmHg)	6.3 (2.7, 10)	7.7 (4.3, 10.8)	8.6 (5.9, 12.5)	7.2 (5.3, 13.8)	0.11
Steroid use	19 (47.5%)	10 (14.1%)	16 (16.4%)	17 (35.4%)	0.001
CNI use	3 (7.5%)	4 (5.6%)	0 (0%)	0 (0%)	0.13
eGFR (ml/min/1.73m^2)	85.9 (45.9, 107)	81.4 (65.2,98.2)	52 (33.9, 82.4)	62.2 (36.9, 95.3)	<0.0001
UPC (g/g)	0.78 (0.1, 3.3)	4.3 (2.5, 7.2)	2.2 (0.97, 3.5)	1.4 (0.6, 3.0)	<0.0001
	Pediatric				
	N = 69	N = 2	N = 49	N = 8	
Hypertensive BP status *	31 (44.9%)	1 (50%)	23 (46.9%)	5 (62.5%)	0.91
Hypertensive Uncontrolled *	9 (45%)	1 (50%)	6 (12.2%)	2 (10%)	0.5
SBP (mmHg) †	107 (100, 116)	121.5	112 (102, 118.5)	124.5 (105, 133)	0.13
DBP (mmHg) †	66 (60, 74.5)	77.5	71 (61, 77)	70 (63.8, 80.3)	0.56
SBP Index	0.92 (0.87, 1.0)	0.97	0.90 (0.85, 0.99)	1.0 (0.93, 1.1)	0.6
DBP Index	0.91 (0.80, 1.0)	0.96	0.90 (0.79, 1.0)	0.88 (0.84, 1.0)	0.84
SBP SD (mmHg)	6.4 (3.6, 9.4)	9.6	7.1 (5, 10.4)	8.3 (5.6, 12.7)	0.41
DBP SD mmHg)	6.5 (4.2, 9.9)	8.9	7.1 (4.1, 12.5)	7 (3, 9.4)	0.78
SBP ARV (mmHg)	7 (4, 11)	9.5	9 (6, 11.9)	9.1 (6.6, 11.8)	0.28
DBP ARV (mmHg)	98 (5, 11.2)	9	8.4 (6, 14.4)	7.8 (3.9, 9.1)	0.49

Characteristics N (%) or Median (IQR)	Adult				
	MCD N = 40	MN N = 71	FSGS N = 98	IgA N = 48	p-value
Steroid use	49 (71%)	1 (50%)	34 (69.4%)	3 (37.5%)	0.02
CNI use	18 (26.1%)	1 (50%)	16 (32.7%)	2 (25%)	0.4
eGFR (ml/min/1.73m^2)	110.4 (92, 133)	118.3	89.5 (77, 110.7)	65.6 (55.8, 98.9)	<0.0001
UPC (g/g)	0.39 (0.1, 4.2)	2.3	2.4 (0.68, 5.9)	1.2 (0.17, 5.0)	0.34

*Hypertensive BP status defined as prior diagnosis of hypertension or elevated BP for age at the baseline visit; Hypertensive Uncontrolled defined as prior diagnosis of hypertension and elevated BP at the baseline visit.

†SBP/DBP index- BP was divided by the 95th percentile BP in children

MCD- minimal change disease; MN – membranous nephropathy; FSGS – focal segmental glomerulosclerosis; IgA – IgA nephropathy; BP – BP at baseline; SBP – systolic BP; DBP – diastolic BP; SD – standard deviation; ARV – average real variability; ; CNI – calcineurin inhibitor; eGFR – estimated glomerular filtration rate; UPC – urine protein:creatinine ratio

Table 3

Adjusted Odds Ratios of Baseline Hypertensive Blood Pressure Status by Disease Cohort

Disease Cohort	Adult		Pediatric	
	OR (95% CI)	p-value	OR (95% CI)	p-value
MCD	Ref		Ref	
MN	1.8 (0.62, 5)	0.29	-	-
FSGS	3.8 (1.4, 10.9)	0.01	0.86 (0.35, 2.1)	0.73
IgA	5.5 (1.7, 18)	0.005	1.8 (0.3,10)	0.53
Other	2.3 (0.68, 7.5)	0.18	0.7 (0.2, 2.5)	0.59

MCD- minimal change disease; MN – membranous nephropathy; FSGS – focal segmental glomerulosclerosis; IgA – IgA nephropathy. MN excluded from the pediatric cohort.

Model adjusted for age, sex, race, weight status, edema, steroids, calcineurin inhibitors, estimated glomerular filtration rate, and smoking (adults).

Table 4

Association of Hypertensive Blood Pressure Status at Baseline and Blood Pressure Variability over the First Year with Clinical Outcomes in Adults Enrolled in NEPTUNE

Outcome	β	95% CI	*P* value
eGFR Slope (mL/min/year**)**			
HTN			
Model 1	−0.92	(−3.28, 1.45)	0.45
Model 2	2.07	(−2.51, 6.65)	0.38
SBP SD			
Model 1	0.06	(−0.1, 0.22)	0.44
Model 2	0.08	(−0.08, 0.23)	0.35
DBP SD			
Model 1	0.00	(−0.22, 0.21)	0.98
Model 2	0.01	(−0.2, 0.23)	0.91
SBP ARV			
Model 1	0.04	(−0.09, 0.18)	0.52
Model 2	0.05	(−0.08, 0.19)	0.43
DBP ARV			
Model 1	−0.06	(−0.24, 0.13)	0.55
Model 2	−0.05	(−0.23, 0.13)	0.61

	HR	95% CI	*P* value
Complete Remission Ever (UPC < 0.3)			
HTN			
Model 1	0.36	(0.19, 0.68)	<0.001
Model 2	0.48	(0.29, 0.80)	<0.001
SBP SD			
Model 1	1.01	(0.98,1.04)	0.41
Model 2	1.03	(0.99, 1.07)	0.10
DBP SD			
Model 1	1.01	(0.98, 1.03)	0.55
Model 2	1.02	(0.99, 1.05)	0.13
SBP ARV			
Model 1	1.00	(0.96, 1.04)	0.92
Model 2	1.01	(0.96, 1.07)	1.01
DBP ARV			
Model 1	0.98	(0.94, 1.01)	0.19
Model 2	0.99	(0.94, 1.03)	0.55
Composite Endpoint (ESRD or eGFR decline <40%)			
HTN			
Model 1	4.11	(1.41, 12.02)	0.01

	HR	95% CI	*P* value
Model 2	1.40	(0.71, 2.76)	0.33
SBP SD *			
Model 1	1.05	(1.02, 1.09)	<0.001
DBP SD *			
Model 1	1.04	(1.01, 1.07)	0.01
SBP ARV *			
Model 1	1.10	(1.02, 1.18)	0.01
DBP ARV *			
Model 1	1.08	(1.04, 1.12)	<0.001

Model 1: Includes age at baseline, sex, race, disease cohort and follow up time

Model 2: Includes Model 1 + smoking status, CNI/steroid use, RAAS use, weight status, edema, cholesterol, SBP index and eGFR.

* Model 2 failed to converge (i.e. there was no maximum to the maximum likelihood function since there were variables in which there were no observations for exposure levels amongst the cases and/or controls.)

HTN – hypertensive blood pressure status; eGFR- estimated glomerular filtration rate; UPC – urine protein creatinine; SBP – systolic blood pressure; DBP – diastolic blood pressure; SD – standard deviation; ARV – average real variability; ESRD – end stage renal disease

Table 5

Association of Hypertensive Blood Pressure Status at Baseline and Blood Pressure Variability over the First Year with Clinical Outcomes in Children Enrolled in NEPTUNE

Outcome	β	95% CI	*P* value
eGFR Slope (mL/min/year**)**			
HTN			
Model 1	−0.17	(−2.95, 2.62)	0.91
Model 2	2.07	(−2.51, 6.65)	0.38
SBP SD			
Model 1	−0.41	(−1.12, 0.31)	0.27
Model 2	−0.58	(−1.4, 0.24)	0.17
DBP SD			
Model 1	−0.34	(−1.17, 0.49)	0.43
Model 2	−0.36	(−0.96, 0.1)	0.11
SBP ARV			
Model 1	−0.32	(−0.84, 0.2)	0.23
Model 2	−0.43	(−1.27, 0.54)	0.44
DBP ARV			
Model 1	−0.41	(−0.95, 0.14)	0.14
Model 2	−0.37	(−0.91, 0.17)	0.18

	HR	95% CI	*P* value
Complete Remission Ever (UPC < 0.3)*			
HTN			
Model 1	0.51	(0.26, 1.01)	0.05
SBP SD			
Model 1	0.96	(0.91, 1.01)	0.11
DBP SD			
Model 1	1.00	(0.95, 1.04)	0.89
SBP ARV			
Model 1	0.92	(0.87, 0.98)	0.01
DBP ARV			
Model 1	0.95	(0.90, 1.00)	0.04
Composite Endpoint (ESRD or eGFR decline <40%)*			
HTN			
Model 1	1.23	(0.42, 3.59)	0.71
SBP SD			
Model 1	1.10	(1.03, 1.09)	<0.001
DBP SD			
Model 1	1.05	(0.99, 1.12)	0.09
SBP ARV			

	HR	95% CI	*P* value
Model 1	1.10	(1.02, 1.18)	0.01
DBP ARV			
Model 1	1.03	(0.97, 1.09)	0.30

Model 1: Includes age at baseline, sex, race, disease cohort, and follow up time

Model 2: Includes Model 1 + CNI/steroid use, RAAS use, weight status, edema, cholesterol, SBP index and eGFR.

*Model 2 failed to converge (i.e. there was no maximum to the maximum likelihood function since there were variables in which there were no observations for exposure levels amongst the cases and/or controls.)

HTN – hypertensive blood pressure status; eGFR- estimated glomerular filtration rate; UPC – urine protein creatinine; SBP – systolic blood pressure; DBP – diastolic blood pressure; SD – standard deviation; ARV – average real variability; ESRD – end stage renal disease