Epidemiology/Population

Modification of the Relationship Between Blood Pressure and Renal Albumin Permeability by Impaired Excretory Function and Diabetes

James Fotheringham, Aghogho Odudu, William McKane, Timothy Ellam

Abstract—In animal models, reduced nephron mass impairs renal arteriolar autoregulation, increasing vulnerability of the remaining nephrons to elevated systemic blood pressure (BP). A feature of the resulting glomerular capillary hypertension is an increase in glomerular permeability. We sought evidence of a similar remnant nephron effect in human chronic kidney disease. In participants from the United States National Health and Nutrition Examination Surveys 1999 to 2010 (N=23710), we examined the effect of reduced estimated glomerular filtration rate (eGFR) on the relationship between brachial artery BP and albumin permeability. Renal albumin permeability increased exponentially with systolic BP >110 mmHg, and this association was modified by independent interactions with both excretory impairment and diabetes mellitus. Each 10 mmHg increase in systolic BP was accompanied by an increase in fractional albumin excretion of 1.10-, 1.11-, 1.17-, 1.22-, and 1.38-fold for participants with eGFR=90, 90>eGFR=60, 60>eGFR=45, 45>eGFR=30, and eGFR<30 mL/min/1.73 m², respectively, adjusted for age, sex, race, antihypertensive use, eGFR category, diabetes mellitus, smoking, history of cardiovascular disease, body mass index, and C-reactive protein. A 10 mmHg systolic BP increment was associated with increases in fractional albumin excretion of 1.10- and 1.21-fold in nondiabetic and diabetic participants, respectively. Using urine albumin creatinine ratio as an alternative measure of albumin leak in eGFR-adjusted analyses gave the same conclusions. Our findings are consistent with the presence of a remnant nephron effect in human kidney disease. Future trials should consider the nephroprotective benefits of systolic BP lowering in kidney disease populations stratified by eGFR. (Hypertension. 2015;65:510-516. DOI: 10.1161/HYPERTENSIONAHA.114.04656.) • Online Data Supplement

Key Words: albuminuria • autoregulation • blood pressure • diabetes mellitus • eGFR

Hypertension accelerates the progression of chronic kidney disease (CKD) and controlling blood pressure (BP) is the mainstay of general CKD management. In animal models, a remnant nephron effect has been described, whereby a reduction in nephron mass results in increased transmission of systemic hydrostatic pressure to the glomerular microcirculation, accompanied by increased glomerular permeability, proteinuria, and progressive renal injury. Operation of a similar phenomenon in human CKD is implied by the fact that faster CKD progression is associated with BP increments that in isolation rarely initiate significant loss of excretory function. However, the relationship between nephron loss and vulnerability to hypertensive damage in humans is poorly defined; it is unknown whether there is a threshold level of excretory impairment at which BP increments are more likely to overcome renal autoregulation and induce further injury. Antihypertensive trials have not reported effects on hard renal end points stratified by baseline function and so guidelines do not differentiate CKD BP targets on the basis of estimated glomerular filtration rate (eGFR).

Increased glomerular albumin leak is a feature of hypertensive renal end-organ damage, and there is some evidence that CKD patients with heavier proteinuria benefit from lower BP targets. It is postulated that these observations reflect an increase in glomerular permeability caused by elevated glomerular capillary hydrostatic pressure. We sought evidence of a human remnant nephron effect increasing the transmission of BP to the glomerular microcirculation and modulating the relationship between increasing BP and albumin permeability. Specifically, we hypothesized that at lower levels of excretory function, a given BP increment would be associated with a greater relative increase in renal albumin permeability. This hypothesis was tested in a representative sample of the US population: the National Health and Nutrition Examination Survey (NHANES) 1999 to 2010. Fractional excretion of albumin (Fₑalb, relative to creatinine) was used as the primary measure of albumin permeability; because a given albumin leak occurring across a reduced nephron mass must indicate a greater degree of albumin permeability, Fₑalb is a more logical measure of renal albumin permeability than the total urine albumin:creatinine ratio (ACR).

Diabetes mellitus, like reduced nephron mass, is considered to increase the transmission of systemic pressure to the glomerular microcirculation, accompanied by increased glomerular permeability, proteinuria, and progressive renal injury. In animal models, reduced nephron mass impairs renal arteriolar autoregulation, increasing vulnerability of the remaining nephrons to elevated systemic blood pressure. A feature of the resulting glomerular capillary hypertension is an increase in glomerular permeability. We sought evidence of a similar remnant nephron effect in human chronic kidney disease.
glomerulus and sensitize to hypertensive renal injury. The extent to which diabetes mellitus is accompanied by a greater relative increase in FE\textsubscript{ab} for a given BP increment was therefore also studied.

Methods

Study Population

The US NHANES uses a multistage sampling strategy to create a survey cohort representative of the noninstitutionalized US population. Oversampling of demographic subgroups (non-Hispanic Blacks, Mexican Americans, and those aged >60 years) increases the reliability of prevalence estimates in these groups, and sample weights are assigned to relate the selected sample to the US population.

For this analysis, data were combined from nonpregnant participants in the NHANES cycles 1999 to 2010 attending a mobile examination center. Participants aged ≥20 years with complete data for BP, weight, height, serum and urine albumin and creatinine, smoking status, diabetes mellitus status, and history of cardiovascular disease were included. Diabetes mellitus was defined as a response Yes to the question, Have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes or current use of insulin or oral hypoglycemic agents. Current smoking status was classified according to the question, Have you used tobacco or nicotine in the last 5 days, and a history of cardiovascular disease was defined by Yes to Have you ever been told you had coronary heart disease/angina/heart attack. Race and ethnicity were self-reported and were categorized for analysis as non-Hispanic White, non-Hispanic Black, Hispanic, or other. Age was categorized into 10 years intervals. Antihypertensive medication constituents were classified using the Lexicon Plus (Cerner Multum Inc.) drug database.

The Research Ethics Review Board of the National Center for Health Statistics approved the NHANES data collection procedures, and written consent was obtained from all participants.

Measurements

Blood pressure was measured in a sitting position after 5 minutes quiet resting using a mercury sphygmomanometer. After ascertainment of the maximal inflation level by radial artery palpation, 3 pairs of systolic/diastolic BP measurements were taken and a fourth attempted if ≥1 were unsuccessful. The average of the readings was used, with exclusion of the first successful reading. Where only 1 reading was successful, this was taken as the average. A value of zero was not allowed in this analysis. Further details of the BP measurement protocol are provided in the NHANES Examination Procedures Manual. Body mass index was calculated as weight/height\textsuperscript{2} and categorized into intervals separated by established cut points of 18.5, 25, 30, 35, and 40 kg/m\textsuperscript{2}.

A venous blood sample and a random clean-catch urine sample were obtained, allowing calculation of FE\textsubscript{ab} as (urine albumin concentration × serum creatinine concentration)/(urine creatinine concentration × serum albumin concentration). Urine ACR was also calculated and used as an estimate of total renal albumin excretion rate.

Serum creatinine concentration was recalibrated across cycles\textsuperscript{15} and the Chronic Kidney Disease Epidemiology Equation\textsuperscript{16} eGFR categorized using cut points at 90, 60, 45, and 30 mL/min/1.73 m\textsuperscript{2}.

Statistical Analyses

Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) incorporating participant sample weights as per NHANES analytic guidelines. Taylor series linearization was used to estimate standard errors, accounting for the sampling design. Characteristics of the US population represented by NHANES participants were compared across eGFR categories by linear and logistic regression models (combined systolic and diastolic 2-slopes model for increasing BP). This approach performed better than single-slope regression for each BP component and in the combined models (combined systolic and diastolic 2-slopes model for FE\textsubscript{ab} R\textsuperscript{2}=0.104 versus single slopes model R\textsuperscript{2}=0.089). Back-transformed coefficients from these models are shown in Table 2. Increases in FE\textsubscript{ab} and ACR accompanying systolic BP increments >110 mm Hg remained highly significant (P<0.001) when adjusted for sex, age, race, eGFR, C-reactive protein, diabetes mellitus, body mass index, number of antihypertensives, angiotensin-converting enzyme inhibitor use, angiotensin receptor blocker use, use of renin antagonists, and history of cardiovascular disease.

In the unadjusted model, increasing diastolic BP at <70 mm Hg was accompanied by a significantly lower FE\textsubscript{ab} and ACR. However, adjustment for eGFR and age (both predictors of pulse pressure and albumin leak in univariate model associations between BP and albuminuria. Adjustment was then made a priori for relevant covariates: age, sex, race, diabetes mellitus, body mass index category, eGFR category, smoking status, C-reactive protein, number of antihypertensives prescribed, use of angiotensin-converting enzyme inhibitors, use of angiotensin receptor blockers, use of renin antagonists, and history of cardiovascular disease.

Categorization of systolic BP into 10 mm Hg categories was also applied to define the thresholds at which increased systolic BP was associated with greater FE\textsubscript{ab} and ACR in subpopulations with eGFR≥70 or <60 mL/min/1.73 m\textsuperscript{2} and with/without diabetes mellitus.

To determine whether excretory impairment and diabetes mellitus interact with systolic BP increments in predicting FE\textsubscript{ab} product terms for eGFR category × systolic BP and diabetes mellitus × systolic BP were added into the regression model, with covariate adjustments as listed above.

Results

Study Population Characteristics

Of the 29563 nonpregnant participants aged ≥20 years attending a mobile examination center, 23710 had complete demographic, examination, and laboratory data. Characteristics of the US population represented by these participants are shown according to eGFR category in Table 1. In univariate analyses, lower eGFR was accompanied by higher systolic BP, lower diastolic BP, and greater pulse pressure. Median urine ACR was 1.0-, 1.5-, 2.7-, and 13.3-fold greater at 90>eGFR≥60, 60>eGFR≥45, 45>eGFR≥30, and eGFR<30 c.f. eGFR≥90 mL/min/1.73 m\textsuperscript{2}, respectively. The accompanying increases in FE\textsubscript{ab} were 1.2-, 2.2-, 5.6-, and 51.2-fold. Thus, predictably, increases in total albuminuria observed at lower eGFR signify a much greater increase in albumin permeability because more albumin must leak per functioning nephron.

BP and Measures of Renal Albumin Leak

Both FE\textsubscript{ab} and ACR were positively skewed and were log-transformed for parametric analyses. In univariate analysis, log-transformed FE\textsubscript{ab} and ACR increased progressively with increasing systolic pressure >110 mm Hg, whereas diastolic BP showed a bimodal relationship to FE\textsubscript{ab}/ACR with a nadir at 70 mm Hg (shown for FE\textsubscript{ab} in Figure 1).

Considering these findings and with a view to maintaining a parsimonious model that could be interpreted in clinical terms, the relationships between BP and FE\textsubscript{ab}/ACR were examined using 2-slope linear regression models with inflection points at 110 mm Hg for systolic BP and 70 mm Hg for diastolic BP. This approach performed better than single-slope regression for each BP component and in the combined models (combined systolic and diastolic 2-slopes model for FE\textsubscript{ab} R\textsuperscript{2}=0.104 versus single slopes model R\textsuperscript{2}=0.089). Back-transformed coefficients from these models are shown in Table 2. Increases in FE\textsubscript{ab} and ACR accompanying systolic BP increments >110 mm Hg remained highly significant (P<0.001) when adjusted for sex, age, race, eGFR, C-reactive protein, diabetes mellitus, body mass index, number of antihypertensives, angiotensin-converting enzyme inhibitor use, angiotensin receptor blocker use, renin inhibitor use, smoking status, and history of cardiovascular disease.

In the unadjusted model, increasing diastolic BP at <70 mm Hg was accompanied by a significantly lower FE\textsubscript{ab} and ACR. However, adjustment for eGFR and age (both predictors of pulse pressure and albumin leak in univariate
analyses) abolished this association and revealed significant positive associations of increasing diastolic BP >70 mm Hg with FE alb and ACR. Pulse pressure was not itself included as a covariate in the adjusted models because, although increments at >40 mm Hg were associated with increases in FE alb/ACR, pulse pressure was not an independent predictor in models containing systolic and diastolic BP.

Modification of the Relationship Between Systolic BP and Renal Albumin Leak by Excretory Impairment and Diabetes Mellitus

Because systolic BP showed the most consistent association with measures of albumin leak, we examined the interactions of excretory impairment and diabetes mellitus with the systolic BP–FEalb relationship. First, we determined whether there were different thresholds at which systolic BP increments were accompanied by increasing FE alb in participants with and without excretory impairment or diabetes mellitus. To this end, linear regression was performed with systolic BP entered as a separate categorical variable (in 10 mm Hg intervals) for participants with eGFR ≥ 60 versus <60 mL/min/1.73 m² and, in a second model, with versus without diabetes mellitus. The back-transformed coefficients for each systolic BP category from these models are presented in Figure 2. Among participants with eGFR ≥ 60 mL/min/1.73 m², increments in systolic BP were associated with increases in FEalb that were statistically significant for all categories ≥120 mm Hg (versus Table 1. Characteristics of the US Population Represented by NHANES 1999 to 2010 Participants by eGFR Category

<table>
<thead>
<tr>
<th>Variable</th>
<th>eGFR Category, mL/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, n</td>
<td>≥90</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>Male, %</td>
<td></td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>65.6 (1.4)</td>
</tr>
<tr>
<td>Black</td>
<td>11.9 (0.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>16.7 (1.1)</td>
</tr>
<tr>
<td>Other</td>
<td>5.8 (0.4)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>118.6 (0.2)*</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>71.3 (0.2)</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>47.3 (0.2)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>107.7 (0.2)</td>
</tr>
<tr>
<td>ACR, mg/g, geometric mean (95% CI)§</td>
<td>7.0 (6.9, 7.1)</td>
</tr>
<tr>
<td>FEalb, ×10⁻⁷, geometric mean (95% CI)§</td>
<td>12.7 (12.4, 13.0)</td>
</tr>
<tr>
<td>Antihypertensive use, %</td>
<td>12.7 (0.5)</td>
</tr>
<tr>
<td>Diabetic, %</td>
<td>5.4 (0.2)</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>34.6 (0.8)</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>2.6 (0.1)</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>0.38 (0.01)</td>
</tr>
</tbody>
</table>

Data presented as mean (SE) and % (SE) unless otherwise indicated. Comparisons between groups performed by linear and logistic regression for means and proportions, respectively.

ACR indicates albumin:creatinine ratio; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FEalb, fractional excretion; and NHANES, National Health and Nutrition Examination Survey.

*P<0.001 versus eGFR≥90.
†P<0.005 versus eGFR≥90.
‡P<0.05 versus eGFR≥90.
§Positively skewed and log-transformed for regression.
interaction between excretory impairment and systolic BP, evident at eGFR<60 mL/min/1.73 m²; each 10 mmHg increase in systolic BP was accompanied by a further adjusted increase in FEab of 1.01-, 1.07-, 1.11-, and 1.26-fold for participants with 90>eGFR≥60, 60>eGFR≥45, 45>eGFR≥30, and eGFR<30 mL/min/1.73 m², respectively. Thus, the total increment in FEab associated with a systolic BP increase of 10 mmHg (multiplying the above coefficients) was 1.10-, 1.11-, 1.17-, 1.22-, and 1.38-fold at eGFR<30, 90>eGFR≥60, 60>eGFR≥45, 45>eGFR≥30, and eGFR<30 mL/min/1.73 m², respectively.

In the presence of diabetes mellitus, there was a further 1.10-fold increase in FEab associated with each 10 mmHg systolic BP increment. This equates to increases in FEab of 1.10- and 1.21-fold per 10 mmHg systolic BP for nondiabetic versus diabetic participants at eGFR<30 mL/min/1.73 m²; at eGFR<30 mL/min/1.73 m², the increases were 1.38- and 1.51-fold, respectively. There was no evidence of synergism between excretory impairment and diabetes mellitus in their interaction with systolic BP; product terms for diabetes mellitus × eGFR category × systolic BP were not significant when added to the model (not shown).

The findings with regard to ACR were the same as with FEab (Table 3). To confirm that the interaction between excretory impairment and systolic BP was not confounded by the greater

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Table 2. Linear Regression Models of the Relationship Between BP Components and Measures of Renal Albumin Leak

<table>
<thead>
<tr>
<th>BP Category</th>
<th>Fold-Change per 1 SD Increase in BP Component* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td>FEab</td>
</tr>
<tr>
<td>Systolic &lt;110 mmHg</td>
<td>0.94 (0.84, 1.05); P=0.28</td>
</tr>
<tr>
<td>Systolic ≥110 mmHg</td>
<td>1.58 (1.53, 1.63); P=0.001</td>
</tr>
<tr>
<td>Diastolic &lt;70 mmHg</td>
<td>0.88 (0.84, 0.92); P=0.001</td>
</tr>
<tr>
<td>Diastolic ≥70 mmHg</td>
<td>1.02 (0.97, 1.06); P=0.51</td>
</tr>
</tbody>
</table>

Adjusted model†

| Systolic <110 mmHg | 0.95 (0.84, 1.04); P=0.22 | 0.93 (0.84, 1.04); P=0.23 |
| Systolic ≥110 mmHg | 1.29 (1.25, 1.32); P=0.001 | 1.30 (1.26, 1.33); P=0.001 |
| Diastolic <70 mmHg | 1.01 (0.98, 1.05); P=0.57 | 1.01 (0.98, 1.05); P=0.53 |
| Diastolic ≥70 mmHg | 1.14 (1.09, 1.19); P=0.001 | 1.13 (1.09, 1.18); P=0.001 |

Variable Effects of diabetes mellitus and eGFR in the adjusted model†; fold change

| Diabetes mellitus | 1.88 (1.75 2.02); P=0.001 | 1.90 (1.76, 2.04); P=0.001 |
| 60>eGFR≥90‡ | 1.12 (1.08, 1.16); P=0.001 | 0.88 (0.84, 0.91); P=0.001 |
| 45>eGFR≥60‡ | 1.64 (1.49, 1.81); P=0.001 | 0.97 (0.88, 1.07); P=0.40 |
| 30>eGFR≥45‡ | 3.63 (2.99, 4.49); P<0.001 | 1.61 (1.34, 1.95); P<0.001 |
| eGFR<30‡ | 27.60 (17.91, 42.53); P<0.001 | 6.68 (4.55, 9.82); P<0.001 |

ACR indicates albumin:creatinine ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; and FEab, fractional excretion.

*19.5 mmHg systolic and 12.5 mmHg diastolic.
†Covariates in the adjusted model: systolic and diastolic BP (2-slope model), age, sex, race, diabetes mellitus, eGFR category, BMI, C-reactive protein, history of cardiovascular disease, number of prescribed antihypertensives, use of angiotensin-converting enzyme inhibitors, use of angiotensin receptor blockers, use of renin inhibitors, and smoking status.
‡c.f. eGFR<90 mL/min/1.73 m².
prevalence of diabetes mellitus in participants with low eGFR, the analysis was repeated with exclusion of diabetic participants; this did not materially change the findings (not shown). The interaction between excretory impairment and systolic BP also did not seem to reflect a modifying effect of the greater prevalence of antihypertensive use or cardiovascular disease in participants with lower eGFR; interaction terms for antihypertensives, use of angiotensin converting enzyme inhibitors, use of angiotensin receptor blockers, use of renin inhibitors and smoking status.

ACR indicates albumin:creatinine ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; FE_{alb}, Fractional excretion of albumin.

Model adjusted for systolic and diastolic BP (2-slope model), age, sex, race, diabetes mellitus, eGFR, BMI, C-reactive protein, history of cardiovascular disease, number of prescribed antihypertensives, use of angiotensin converting enzyme inhibitors, use of angiotensin receptor blockers, use of renin inhibitors and smoking status.

Further increment from interactions:

(60≤eGFR<90) × systolic BP 1.10 (1.06, 1.12); 1.11 (1.09, 1.13); P<0.001

(45≤eGFR<60) × systolic BP 1.09 (1.06, 1.12); 1.06 (1.03, 1.11); P=0.004

(30≤eGFR<45) × systolic BP 1.11 (1.02, 1.21); 1.11 (1.02, 1.20); P=0.015

(eGFR<30) × systolic BP 1.26 (1.09, 1.45); 1.23 (1.09, 1.40); P=0.002

Diabetes mellitus × systolic BP 1.10 (1.06, 1.15); 1.09 (1.05, 1.14); P<0.001

Model adjusted for systolic and diastolic BP (2-slope model), age, sex, race, diabetes mellitus, eGFR, BMI, C-reactive protein, history of cardiovascular disease, number of prescribed antihypertensives, use of angiotensin converting enzyme inhibitors, use of angiotensin receptor blockers, use of renin inhibitors and smoking status.

ACR indicates albumin:creatinine ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; FE_{alb}, Fractional excretion of albumin.

Model adjusted for systolic and diastolic BP (2-slope model), age, sex, race, diabetes mellitus, eGFR, BMI, C-reactive protein, history of cardiovascular disease, number of prescribed antihypertensives, use of angiotensin converting enzyme inhibitors, use of angiotensin receptor blockers, use of renin inhibitors and smoking status.

ACR indicates albumin:creatinine ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; FE_{alb}, Fractional excretion of albumin.

Model adjusted for systolic and diastolic BP (2-slope model), age, sex, race, diabetes mellitus, eGFR, BMI, C-reactive protein, history of cardiovascular disease, number of prescribed antihypertensives, use of angiotensin converting enzyme inhibitors, use of angiotensin receptor blockers, use of renin inhibitors and smoking status.

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Model adjusted for systolic and diastolic BP (2-slope model), age, sex, race, diabetes mellitus, eGFR, BMI, C-reactive protein, history of cardiovascular disease, number of prescribed antihypertensives, use of angiotensin converting enzyme inhibitors, use of angiotensin receptor blockers, use of renin inhibitors and smoking status.

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Model adjusted for systolic and diastolic BP (2-slope model), age, sex, race, diabetes mellitus, eGFR, BMI, C-reactive protein, history of cardiovascular disease, number of prescribed antihypertensives, use of angiotensin converting enzyme inhibitors, use of angiotensin receptor blockers, use of renin inhibitors and smoking status.

ACR indicates albumin:creatinine ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; FE_{alb}, Fractional excretion of albumin.
common occurrence than end-stage renal disease. Potential increased nephroprotective effects of systolic BP control at lower eGFR must therefore be considered in the context of macrovascular risks and benefits.

With regard to adding excretory function to CKD BP management algorithms alongside albuminuria, there is another issue that may be important and is highlighted by our findings: For a given total albumin excretion rate, subjects with reduced functioning nephron mass must have greater renal albumin permeability. The relationship between changes in ACR and FE_{\text{alb}} across the range of excretory function in the NHANES cohort is predictable, but demonstrates the difference between assessments of total albumin excretion rate and albumin permeability. In the absence of excretory impairment, a greater creatinine clearance is reported to be accompanied by a proportional increase in albumin excretion rate. This is what would be expected with normal albumin permeability, where increased filtration rate will reflect a greater convective driving force or diffusion area for albumin efflux. The prognostic/pathogenic implications of albumin permeability versus absolute albumin excretion are uncertain. However, to our knowledge, no explanation has been proposed which would make total albumin excretion rate a more logical assessment of intrarenal pathophysiology (and BP targets) than albumin permeability.

Measuring the fractional excretion of a marker that does not freely cross the glomerular filtration barrier is the standard approach for assessing glomerular permselectivity. We used the fractional excretion of albumin relative to creatinine, which is readily determined from paired serum and urine samples. Because albumin undergoes reabsorption in the proximal tubule, FE_{\text{alb}} is admittedly not purely a measure of glomerular permeability, but rather reflects whole nephron albumin leak. Our use of the term permeability with regard to FE_{\text{alb}} must thus technically be interpreted as kidney permeability rather than glomerular permeability. The amount of albumin that is normally filtered and reabsorbed remains controversial, nevertheless, the relationship between albuminuria and BP is generally considered to reflect primarily changes in glomerular permeability. Although an increased relative contribution of tubular creatinine secretion in subjects with more severe excretory impairment may result in an underestimation of permeability increases, there is no reason to suppose this affects the relationship between systolic BP and eGFR-stratified relative changes in FE_{\text{alb}}.

A limitation of this work is the lack of characterization of the causes of CKD, which are clearly an important determinant of FE_{\text{alb}} and may influence the relationship between systolic BP and FE_{\text{alb}}. We also did not have ambulatory BP data or measures of arterial stiffness. However, a strength of the study is the use of a population-representative cohort containing participants with a spectrum of excretory function and mixed diabetes mellitus status, allowing us to determine how these factors affect the systolic-BP/FE_{\text{alb}} relationship.

Perspective
We find that in subjects with low eGFR, a given increment in systolic BP is associated with a greater relative increase in renal albumin permeability. This is consistent with animal models demonstrating vulnerability of the renal microvasculature to elevated BP when nephron mass is reduced. Future trials should examine the benefits of antihypertensive interventions in CKD populations stratified by excretory impairment as well as by albuminuria.

Acknowledgments
We are grateful to the National Health and Nutrition Examination Survey (NHANES) participants, staff, and investigators.

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Disclosures
None.

References


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MODIFICATION OF THE RELATIONSHIP BETWEEN BLOOD PRESSURE AND RENAL ALBUMIN PERMEABILITY BY IMPAIRED EXCRETORY FUNCTION AND DIABETES

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Total number of tables: 1

Short title: excretory function, BP and albumin permeability
Table S1. Interaction between eGFR category, diabetes, systolic BP and renal albumin leak by gender.

<table>
<thead>
<tr>
<th>Systolic BP term</th>
<th>Fold change (95% CI) per 10mmHg systolic BP increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$FE_{alb}$</td>
</tr>
<tr>
<td><strong>Men (n=12,095)</strong></td>
<td></td>
</tr>
<tr>
<td>Whole population coefficient</td>
<td>1.13 (1.09, 1.17) p&lt;0.001</td>
</tr>
<tr>
<td>Further increment from interaction terms</td>
<td></td>
</tr>
<tr>
<td>(60≤eGFR&lt;90) x systolic BP</td>
<td>1.01 (0.98, 1.05) p=0.55</td>
</tr>
<tr>
<td>(45≤eGFR&lt;60) x systolic BP</td>
<td>1.11 (1.03, 1.20) p=0.007</td>
</tr>
<tr>
<td>(30≤eGFR&lt;45) x systolic BP</td>
<td>1.28 (1.08, 1.52) p=0.005</td>
</tr>
<tr>
<td>(eGFR&lt;30) x systolic BP</td>
<td>1.06 (0.83, 1.37) p=0.63</td>
</tr>
<tr>
<td>Diabetes x systolic BP</td>
<td>1.09 (1.02, 1.17) p=0.017</td>
</tr>
<tr>
<td><strong>Women (n=11,615)</strong></td>
<td></td>
</tr>
<tr>
<td>Whole population coefficient</td>
<td>1.09 (1.06, 1.12) p&lt;0.001</td>
</tr>
<tr>
<td>Further increment from interaction terms</td>
<td></td>
</tr>
<tr>
<td>(60≤eGFR&lt;90) x systolic BP</td>
<td>1.00 (0.97, 1.03) p=1.0</td>
</tr>
<tr>
<td>(45≤eGFR&lt;60) x systolic BP</td>
<td>1.06 (1.01, 1.11) p=0.020</td>
</tr>
<tr>
<td>(30≤eGFR&lt;45) x systolic BP</td>
<td>1.08 (0.98, 1.18) p=0.11</td>
</tr>
<tr>
<td>(eGFR&lt;30) x systolic BP</td>
<td>1.34 (1.12, 1.61) p=0.002</td>
</tr>
<tr>
<td>Diabetes x systolic BP</td>
<td>1.13 (1.08, 1.19) p&lt;0.001</td>
</tr>
</tbody>
</table>

Model adjusted for systolic and diastolic BP (2-slope model), age, gender, race, diabetes, eGFR, BMI, CRP, history of cardiovascular disease, number of prescribed antihypertensives, use of ACE inhibitors, use of angiotensin receptor blockers, use of renin inhibitors and smoking status.