AJKD

Original Investigation

Association of Kidney Function and Albuminuria With Prevalent and Incident Hypertension: The Atherosclerosis Risk in Communities (ARIC) Study

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Background: Decreased kidney function and kidney damage may predate hypertension, but only a few studies have investigated both types of markers simultaneously, and these studies have obtained conflicting results.

Study Design: Cross-sectional for prevalent and prospective observational study for incident hypertension.

Setting & Participants: 9,593 participants from the ARIC (Atherosclerosis Risk in Communities) Study, aged 53-75 years in 1996-1998.

Predictors: Several markers of kidney function (estimated glomerular filtration rate using serum creatinine and/or cystatin C and 2 novel markers [β-trace protein and β_2-microglobulin]) and 1 marker of kidney damage (urinary albumin-creatinine ratio [ACR]). Every kidney marker was categorized by its quintiles (top quintile as a reference for estimated glomerular filtration rates and bottom quintile for the rest).

Outcomes: Prevalent and incident hypertension.

Measurements: Prevalence ratios and HRs of hypertension based on modified Poisson regression and Cox proportional hazards models, respectively.

Results: There were 4,378 participants (45.6%) with prevalent hypertension at baseline and 2,175 incident hypertension cases during a median follow-up of 9.8 years. Although all 5 kidney function markers were associated significantly with prevalent hypertension, prevalent hypertension was associated most notably with higher ACR (adjusted prevalence ratio, 1.60 [95% CI, 1.50-1.71] for the highest vs lowest ACR quintile). Similarly, ACR was associated consistently with incident hypertension in all models tested (adjusted HR, 1.28 [95% CI, 1.10-1.49] for top quintile), while kidney function markers demonstrated significant associations in some, but not all, models. Even mildly increased ACR (9.14-14.0 mg/g) was associated significantly with incident hypertension.

Limitations: Self-reported use of antihypertensive medication for defining incident hypertension, single assessment of kidney markers, and relatively narrow age range.

Conclusions: Although all kidney markers were associated with prevalent hypertension, only elevated albuminuria was associated consistently with incident hypertension, suggesting that kidney damage is related more closely to hypertension than moderate reduction in overall kidney function.

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INDEX WORDS: Incident hypertension; prevalent hypertension; kidney filtration markers; albuminuria; kidney damage; decreased kidney function; renal impairment; cohort study.

Hypertension is a chronic cardiovascular condition characterized by elevated arterial blood pressure and affects 78 million US adults older than 20 years, which represents 33.0% of the entire US population.[1] Hypertension causes a series of complications, including kidney and cardiovascular disease.[2] More than 90% of all hypertension cases are considered as primary or essential hypertension,[3] and it is a result of a complex interaction among genetic variants, lifestyles, and environmental factors.[2] Other cases that are caused by identifiable reasons, for example, endocrinologic disorders, are categorized as secondary hypertension.[2]

Although hypertension is an established risk factor for decreased kidney function,[4] some evidence also supports reverse association. Basic research studies have shown that subtle kidney injuries may predict elevated blood pressure in rats. The number of nephrons is lower in some animal models with hypertension compared with those without hypertension.[5-8] Similar results were observed in humans using data from casualties of traffic accidents or in the context of premature infants.[9-11] Several epidemiologic studies have investigated the association of kidney function

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and damage with risk for hypertension.[12-18] Most of those studies focused on albuminuria, a marker of kidney damage.[12-16] To our knowledge, only 2 studies investigated markers for both kidney function and damage and obtained conflicting results. One reported a stronger association with albuminuria than kidney function,[14] whereas the other showed a closer association with kidney function.[12]

The primary objective of this study was to investigate the relationship of kidney function and damage markers with incident hypertension in the ARIC (Atherosclerosis Risk in Communities) Study. Given more limited evidence for kidney function in this context, we tested various kidney function markers, including glomerular filtration rate (GFR) estimated by 3 equations based on serum creatinine and/or cystatin C levels shown to have better accuracy than conventional equations[18,19] and 2 novel markers (β-trace protein [BTP] and β_2-microglobulin [B2M]).[20-22] Recognizing potential bidirectional association, we also assessed their associations with prevalent hypertension at baseline.

METHODS

Participants

The ARIC Study is a prospective cohort study enrolling 15,792 participants aged 45-64 years from 4 US communities (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD) during the baseline examination (1987-1989). Details of the ARIC Study have been described elsewhere previously.[23] For this investigation, 10,890 of 11,656 participants who attended visit 4 (1996-1998) had all the data for the present study, including estimated GFR (eGFR) and albuminuria (Fig 1). We excluded participants with prevalent coronary heart disease (CHD) and heart failure because they may have received drugs with an antihypertensive effect for treatment of these conditions (β-blockers or renin-angiotensin system inhibitors), but not for hypertension. Prevalent CHD at visit 4 was defined as self-reported history of CHD at visit 1 or adjudicated CHD cases between visits 1 and 4. Prevalent heart failure was defined as Gothenburg criteria[24,25] stage 3 at visit 1 or incident heart failure hospitalization between visits 1 and 4. Due to a small number of participants (n = 29), we further excluded those whose race was not black or white (ie, Asian or Native American), leaving a final sample of 9,593 participants. The analysis for BTP and B2M was restricted to 8,982 participants, in whom these novel filtration markers were measured using stored samples.

Measurements

Participant characteristics were recorded at visit 4, unless otherwise specified. Alcohol consumption and smoking status were determined by self-report and were categorized as current versus former/never. Height and weight were measured with the participant in light clothing without shoes. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Diabetes was diagnosed as fasting plasma glucose level ≥ 126 mg/dL (≥7.0 mmol/L), nonfasting glucose level ≥ 200 mg/dL (≥11.1 mmol/L), self-reported physician diagnosis of diabetes, or use of antidiabetic medications. Stroke history refers to prevalent stroke status at visit 1 and any adjudicated cases between visits 1 and 4. Total cholesterol was measured using enzymatic methods. Physical activity level was recorded at visit 3 (1993-1995), and we used a sport index score ranging from 1-5 (1, lowest level of activity; 5, highest level of activity) based on self-reported frequency of exercise and sweating, exercise intensity, and a subjective assessment of physical activity compared with peers with similar age. Information about completed years of education was obtained at visit 1 and was grouped into 3 categories: no/basic (less than high school), intermediate (high school graduate or vocational school), and advanced (college, graduate school, or professional school).

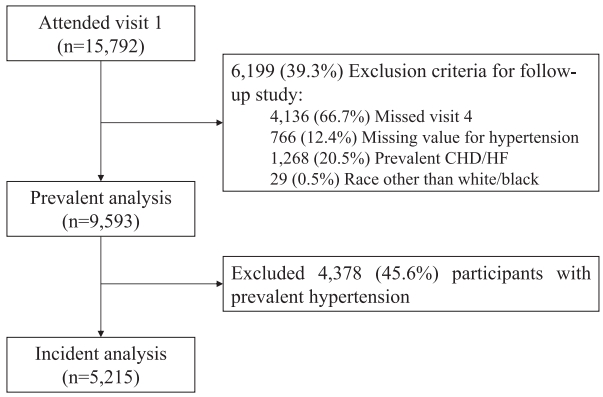

Figure 1. Flow chart of the selection of study participants. Abbreviations: CHD, coronary heart disease; HF, heart failure.

Kidney Function and Damage Markers

For eGFR, we used the best available equations based on serum creatinine and/or cystatin C levels along with demographic variables such as age, sex, and race ($eGFR_{cr\text{-}cys}$, $eGFR_{cr}$, and $eGFR_{cys}$ [race not included in this equation]).[18,19] Our primary kidney function measure was $eGFR_{cr\text{-}cys}$ because this is the best available estimate of measured GFR.[18] A modified kinetic Jaffé method was adapted to measure serum creatinine, and it was standardized to isotope-dilution mass spectrometry–traceable measurements in ARIC visit 4.[26] Serum cystatin C was measured by a particle-enhanced immunonephelometric assay using a BNII nephelometer (Siemens Healthcare Diagnostics). Additionally, serum BTP and B2M were measured by the same nephelometer and were investigated as additional kidney function markers. Reliability coefficients for these novel kidney function markers were greater than 0.94.[22] As recommended in the clinical guidelines,[27] urinary albumin-creatinine ratio (ACR) was used as a measure of kidney damage. Concentrations of urinary albumin and creatinine were determined separately by nephelometry and the Jaffé method, respectively, using spot urine samples.

Definition of Hypertension

Certified technicians measured sitting blood pressure twice 5 minutes apart after a rest using a random-zero sphygmomanometer. The average of the 2 readings was recorded. Prevalent hypertension was defined as systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure (DBP) ≥ 90 mm Hg, or taking any antihypertensive medications at baseline and was used as the outcome variable for cross-sectional analysis. Participants were requested to bring medication containers at baseline and specifically were asked whether they were taking medications for high blood pressure. For those without prevalent hypertension at baseline, incident hypertension was defined as self-reported use of antihypertensive medication from annual follow-up telephone interviews after baseline and was used as the outcome variable for prospective analysis.