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Original Investigation

Midlife Blood Pressure and Late-Life GFR and Albuminuria: An Elderly General Population Cohort

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Background: Chronic kidney disease (CKD) is common in the elderly, but the cause is often not identifiable. Some posit that age-related reductions in glomerular filtration rate (GFR) and increases in albuminuria are normal, whereas others suggest that they are a consequence of vascular disease.

Study Design: Cross-sectional analysis of a substudy of a prospective cohort.

Setting & Participants: AGES (Age, Gene/Environment Susceptibility)−Reykjavik Study.

Predictor: Exposure to higher blood pressure in midlife.

Outcomes & Measurements: Measured GFR using plasma clearance of iohexol and urine albumin-creatinine ratio.

Results: GFR was measured in 805 participants with mean age in midlife and late life of 51.0 ± 5.8 and 80.8 ± 4.0 (SD) years, respectively. Mean measured GFR was 62.4 ± 16.5 mL/min/1.73 m^2 and median albuminuria was 8.0 (IQR, 5.4-16.5) mg/g. Higher midlife systolic and diastolic blood pressures were associated with lower later-life GFRs. Associations persisted after adjustment. Higher midlife systolic and diastolic blood pressures were also associated with higher albumin-creatinine ratios, and associations remained significant even after adjustment.

Limitations: This is a study of survivors, and people who agreed to participate in this study were healthier than those who refused. Blood pressure may encompass effects of the other risk factors. Results may not be generalizable to populations of other races. We were not able to adjust for measured GFR or albuminuria at the midlife visit.

Conclusions: Factors other than advanced age may account for the high prevalence of CKD in the elderly. Midlife factors are potential contributing factors to late-life kidney disease. Further studies are needed to identify and treat midlife modifiable factors to prevent the development of CKD.

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INDEX WORDS: Chronic kidney disease (CKD); elderly; blood pressure; hypertension; measured glomerular filtration rate (mGFR); iohexol clearance; renal function; albuminuria; albumin-creatinine ratio (ACR); mid-life; aging; modifiable risk factor.

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Chronic kidney disease (CKD) is an important health problem in the elderly, with high cost and increased risk for kidney failure, cardiovascular disease, and death.[1] Aging is associated with a decline in glomerular filtration rate (GFR) and an increase in albuminuria, with a CKD prevalence of 47% for those 70 years and older.[2] Some have suggested that the high prevalence of CKD in the elderly is secondary to normal aging,[3] whereas others have hypothesized that vascular disease is a major contributing factor because CKD is commonly seen in the presence of vascular disease or its risk factors.[4-12] Demonstrating that CKD is not inevitable and identifying modifiable risk factors for CKD in the elderly would have important implications for prevention.

Higher blood pressure in particular may play an important role in the development of CKD. The kidney

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is a highly vascular organ with high blood flow and low vascular impedance and is thus subjected to transmission of high pressures into the microcirculation, where excessive pressure may cause damage. Hypertension is common in developed countries, and people with hypertension have been observed to have greater declines in kidney function with aging than those without hypertension, but these studies are limited by small sample size or absence of measured GFR (mGFR).[13-16] Previous studies have documented an association of higher midlife blood pressure with the development of end-stage renal disease in men, but not to decreased GFR per se.[17,18] Thus, the role of blood pressure in midlife on late-life kidney disease is not well understood.

We measured GFR using plasma clearance of iohexol and albuminuria using 2 spot urine samples in older adults participating in the Age, Gene/Environment Susceptibility (AGES)−Reykjavik Study. The AGES-Reykjavik Study is a continuation of the population-based prospective Reykjavik Study that has followed up these participants since midlife and as such provides a good opportunity to examine the association of midlife factors and late life disease. We hypothesized that exposure to higher blood pressure in midlife is an important determinant of lower GFR and higher albuminuria in late life.

METHODS

Study Populations

The AGES-Reykjavik Study originates from the Reykjavik Study, a community-based cohort established in 1967 to prospectively study cardiovascular disease in Iceland. In 2002 to 2006, a total of 5,764 men and women participated in detailed evaluations of cardiovascular, neurocognitive, musculoskeletal, and metabolic phenotypes.[19] The second visit (AGES-II-Reykjavik) was a repeat examination of 3,411 participants (71% of the AGES-Reykjavik survivors) in 2007 to 2011. Of these, 3,341 completed both visit days of the AGES-II-Reykjavik visit and were eligible for inclusion. Of AGES-II-Reykjavik participants, 805 were enrolled in the substudy to measure GFR (AGES-Kidney). For details of selection and exclusion, please see Item S1 (provided as online supplementary material). The study was approved by the Icelandic Bioethics Committee and the institutional review boards at the National Institute on Aging and Tufts Medical Center. All participants gave written informed consent.

GFR Measurements

Details of the GFR measurement procedure can be found in Item S1. The GFR visit occurred a median of 65 (interquartile range [IQR], 32-376) days from the AGES-II-Reykjavik visit day. Five milliliters of iohexol was administered over 30 seconds followed by 10 mL of normal saline solution flush. Blood samples for plasma clearance measurements were taken from a second catheter at approximately 120, 180, 240, and 300 minutes, with the exact times recorded. mGFR was calculated from plasma clearance of iohexol using the Brochner-Mortensen equation[20]; mGFR was expressed per 1.73 m^2 of body surface area.

Albuminuria Measurements

Urine samples were collected at the AGES-II-Reykjavik visit and on the day of GFR measurement. When available, values from these 2 visits were averaged due to the known variation in albuminuria (n = 793). Albuminuria was reported as albumin-creatinine ratio (ACR). For statistical analyses, ACR was log transformed due to its skewness, and parameter estimates from linear regression model were exponentiated and reported as the geometric mean ratio.

Laboratory Methods

All laboratory tests for samples obtained on the day of GFR measurement were performed at the University of Minnesota on samples frozen at −80°C. Iohexol concentration was determined using high-performance liquid chromatography (coefficient of variation, 1.6%). Urine albumin was measured on a nephelometric analyzer (ProSpec; Dade Behring; coefficient of variation, 3.2%). Urine creatinine was measured on a multiple analyzer (Modular P Chemistry Analyzer; Roche Diagnostics; coefficient of variations, 4.3% and 1.5% at concentrations of 18.39 and 96.57 mg/dL, respectively). Urine albumin and creatinine for urine samples collected from participants during the AGES-II-Reykjavik visit were also measured at the University of Minnesota using the mentioned methods. All other laboratory tests performed during the Reykjavik Study or AGES-II-Reykjavik visit were performed at the Icelandic Heart Association laboratory. Serum creatinine during the Reykjavik Study was assayed on continuous flow analyzers (Technicon AutoAnalyzer I, from 1967-1986, SMA-6, from 1986-1988) and a biochemistry analyzer (Cobas-Mira; Roche) thereafter.

Variables

Other variables of interest were age at the GFR visit, blood pressure and hypertension treatment at the midlife and AGES-II-Reykjavik visits, and vascular disease risk factors and cardiovascular disease at the time of the midlife visit. For participants in the Reykjavik Study who had multiple visits, we used the midlife visit as has been used previously.[21-23] At the midlife visit, hypertension was defined as blood pressure > 140/90 mm Hg or use of antihypertensive medications; diabetes was defined as fasting glucose level > 126 mg/dL, random glucose level > 200 mg/dL, or self-report of having a diagnosis of diabetes or being on a diabetic diet or medication use; hyperlipidemia was defined as total cholesterol level > 240 mg/dL; obesity was defined as body mass index > 30 kg/m^2; and smoking was categorized as current, past, or never. Blood pressure was measured using a wall model mercury sphygmomanometer (Erkameter; Erka) after a 5-minute rest. History of cardiovascular disease was defined as prevalent coronary heart disease according to adjudicated Icelandic Heart Association registry or hospital records before the Reykjavik Study midlife visit. GFR was estimated using the 2009 CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[2]

Statistical Analyses

Descriptive data were summarized using mean or median, standard deviation or range, *P* value, and 95% confidence interval (CI). Parallel analyses were performed for the 2 outcomes of mGFR and albuminuria. Both mGFR and albuminuria were considered as continuous variables and categorized according to thresholds used for general populations.[24] Prevalence of CKD was determined by mGFR < 60 mL/min/1.73 m^2 or albuminuria > 30 mg/g.[25]

We used linear regression to examine the relationships between the 2 outcomes and the variables of interest first in univariate models. Systolic and diastolic blood pressure at midlife had the strongest associations with either outcome and were selected as the key factors of interest along with age and sex. For both outcomes, we tested for nonlinearity in the functional relationship of systolic and diastolic blood pressure using parametric cubic polynomials with 4 knots using the rms package in R (R Foundation for Statistical Computing), with $P < 0.05$ from analysis of variance for the nonlinear component of the cubic spline indicating evidence of nonlinearity.[26] At late life, there was a nonlinear relationship with

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