Relations of Measures of Endothelial Function and Kidney Disease: The Framingham Heart Study

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Background: Endothelial dysfunction is prevalent in individuals with end-stage renal disease. Whether endothelial dysfunction is present in patients with moderate chronic kidney disease (CKD) is uncertain.

Study Design: Cross-sectional study.

Settings & Participants: Brachial reactivity measurements were obtained during the seventh examination cycle in 2,818 (diameter measurements) and 2,256 (flow measurements) Framingham Heart Study Offspring cohort participants (53% women; mean age, 61 ± 9 years).

Predictor: Estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 derived from creatinine- and cystatin C–based estimating equations; microalbuminuria status.

Outcome: Brachial reactivity measurements (baseline brachial diameter, flow-mediated dilation, baseline and hyperemic mean flow).

Measurements: Linear regression models were used to model brachial measures as a function of CKD and microalbuminuria status.

Results: Overall, 7.3% (n = 206) of participants had CKD, and of 2,301 with urinary measurements, 10.0% (n = 230) had microalbuminuria. Brachial reactivity measures did not differ significantly by CKD status in either creatinine- or cystatin C–based equations in either age- and sex- or multivariable-adjusted models. In age- and sex-adjusted models, microalbuminuria was associated with decreased hyperemic mean flow (47.2 ± 1.4 versus 51.4 ± 0.5 mg/g; $P = 0.005$), but the association was not significant after multivariable adjustment ($P = 0.09$).

Limitations: Predominantly white ambulatory cohort; results may not be generalizable to other ethnic groups or individuals with severe CKD.

Conclusions: Endothelial dysfunction was not a major correlate of CKD in our sample.

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INDEX WORDS: Chronic kidney disease; brachial reactivity; cystatin C; Framingham Heart Study.

Chronic kidney disease (CKD) affects more than 19 million adults in the United States[1] and is associated with cardiovascular disease (CVD)[2-5] and its risk factors, including diabetes, hypertension, and dyslipidemia.[6,7] The mechanisms involved in the relations between CKD and CVD are not fully understood and may be caused by nontraditional risk factors, including endothelial dysfunction.[8]

Endothelial function is associated with multiple CVD risk factors,[9-13] including hyperlipidemia, hypertension, diabetes, and smoking, and is independently associated with incident CVD events.[10,14,15] In individuals with end-stage renal disease (ESRD), decreased production of nitric oxide has been investigated as a mechanism leading to impaired endothelium-dependent vasodilatation.[16] A recent study of dialysis patients and matched healthy controls attributed the decrease in endothelium-dependent vasodilatation observed in the dialysis patients to nitric oxide impairment.[17] Associations observed between

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measures of endothelial dysfunction and CVD outcomes and all-cause mortality in individuals with ESRD[18-23] suggest that impaired endothelial function may be a key mediator of CVD risk in patients with ESRD. Impaired endothelial function, assessed by using circulating biomarker levels and brachial measures, has been observed in individuals with ESRD compared with referents without known CKD[24-29] and those with less severe forms of CKD.[26,29]

Limited research exists investigating endothelial function in patients with stages 3 and 4 CKD. Impaired endothelium-dependent vasodilatation has been observed in patients with stage 4 CKD,[30] and levels of circulating biomarkers of endothelial dysfunction were increased in patients without diabetes, but with moderate to severe CKD, compared with healthy controls.[31] In a population-based sample from the Hoorn Study, increased levels of circulating biomarkers of endothelial dysfunction were associated with decreasing estimated glomerular filtration rate (eGFR) in participants unselected for CKD.[32] However, less is known about the association of endothelial function and stage 3 CKD. Brachial artery flow-mediated dilation (FMD) is a noninvasive technique that uses ultrasound imaging to measure the degree of endothelial dysfunction.[33] Thus, we sought to test the hypothesis that measures of noninvasively assessed endothelial function are impaired in individuals with stage 3 CKD in the community. We also assessed relations between measures of endothelial function and urinary albumin excretion and cystatin C-based estimating equations.

METHODS

Study Sample

The study design and methods of the Framingham Offspring cohort have been described previously.[34] The Offspring cohort was established in 1971 and was composed of children and spouses of children of the original Framingham cohort. Of 5,124 men and women originally in the Offspring cohort, 3,539 attended the seventh examination cycle (1998-2001), of whom 2,883 had available FMD data and were considered eligible for this study. Participants with missing creatinine data (n = 20), eGFR less than 15 mL/min/1.73 m^2 (<0.25 mL/s/1.73 m^2; n = 3), missing covariate data (n = 20), and urinary albumin-creatinine ratio (UACR) greater than 300 mg/g (n = 22) were excluded from the analysis. After exclusions, 2,818 individuals remained for brachial diameter analyses. Baseline mean flow and hyperemic mean flow were measured in a subset of individuals eligible for this analysis (n = 2,256); flow measurements were introduced partway through the seventh examination cycle. Participants excluded from the analysis tended to be older and were more likely to be women, have diabetes, and be on hypertension treatment. Of those excluded, UACR and cystatin C values were greater (data not shown). Measurements for UACR were available for 2,301 participants, and analyses based on UACR were limited to these individuals; there were no statistically significant differences between participants with and without UACR data.

The Boston University Medical Center (Boston, MA) Institutional Review Board approved this study, and all participants supplied written informed consent.

Measurements and Definitions

Kidney function was determined using eGFR based on the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[35,36] The National Kidney Foundation clinical practice guidelines define CKD as the presence of eGFR less than 60 mL/min/1.73 m^2 (<1 mL/s/1.73 m^2) with or without kidney damage for at least 3 months.[37]

The MDRD Study equation estimates GFR based on an individual's age, sex, race, and serum creatinine level.[35,36] Serum creatinine was measured using the modified Jaffé method from fasting blood samples collected during participants' seventh examination cycle. A 2-step calibration process for serum creatinine was implemented because of potential interlaboratory variability, and this process has been described previously.[38] Briefly, a correction factor of 0.23 mg/dL (20 μmol/L) was applied to National Health and Nutritional Examination Survey III (NHANES III) serum creatinine values to calibrate them to the Cleveland Clinic Laboratory. Our serum creatinine values were then aligned to the age- and sex-specific mean values for serum creatinine levels from NHANES III.

Cystatin C concentrations were measured on previously frozen serum samples (stored at −80°C) by means of nephelometry (Dade Behring Diagnostic, Marburg, Germany) and reported as milligrams per liter. Intra-assay and interassay coefficients of variation were 2.4% and 3.3%, respectively. The range of detection was 0.29 to 7.22 mg/L. Cystatin C was transformed to eGFR by using the following equation: eGFR = 76.7 · cystatin $C^{-1.19}$.[39]

Microalbuminuria was defined as UACR of at least 30 mg/g.[37] Spot urine samples were obtained during the examination and kept at −20°C until quantification. Urinary albumin concentration was assessed using immunoturbimetry (Tina-quant Albumin assay; Roche Diagnostics, Indianapolis, IN). Urinary creatinine was measured by using a modified Jaffé method; the intra-assay coefficient of variation varied from 1.7% to 3.8%. UACR accounts for differences in urine concentrations, has been validated, and is a reliable measure of urinary albumin excretion. UACR also correlated with albumin excretion rates determined using a 24-hour urine collection.[40,41]

FMD Assessment

FMD was assessed as previously described.[13] A Toshiba SSH-140A ultrasound system and 7.5-mHz linear-array transducer (Toshiba Corp, Japan) were used to image the brachial