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Proteinuria in Mid-Life and 39-Year Total Mortality: The Honolulu Heart Program

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proteinuria; urinalysis; mortality; cohort studies; Japanese Americans

INTRODUCTION

Proteinuria is an independent predictor of cardiovascular and total mortality.[1,2] The pathophysiologic mechanisms underlying the association between proteinuria and increased mortality are still poorly understood. Proteinuria is proposed to reflect widespread systemic vascular damage and endothelial disturbance and dysfunction with kidney involvement.[3]

Among proteinuria assessment methods, urine dipstick is commonly used in clinical settings as an initial screening tool because of its low cost, wide availability, and ability to provide quick point-of-care information. The urine dipstick detects urinary protein based on concentration, rather than the absolute quantity, may be influenced by daily variability in urine volume, and false-positive results occur with some health conditions.[4] Therefore,

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CONFLICTS OF INTEREST/DISCLOSURE:

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repeating urine dipstick might be beneficial to increase accuracy in evaluating proteinuria status.

Previous longitudinal population-based studies have examined the relationship between proteinuria by single measurement of urine dipstick and all-cause mortality.[5–7] However, multiple measurements have never been examined and a long-term relationship between dipstick proteinuria and all-cause mortality has never been investigated previously. We examined the relationship between proteinuria based on urine dipstick on two separate occasions and 39-year all-cause mortality.

METHODS

Study design and population

The Honolulu Heart Program is an ongoing prospective epidemiological cohort study of coronary heart disease and stroke established in 1965 in 8,006 Japanese-American men, born between 1900 and 1919, living on Oahu, Hawaii,[8] and recruited from World War II Selective Service Registration files.[9] Details of the study design have been published previously.[10] The Kuakini Medical Center Institutional Review Board approved this study and written informed consent was obtained from all participants at each examination.

Predictor Variable

Urine protein was assessed from urine dipstick tests in 1965–68 and 1971–74. Subjects without urine dipstick results from both examinations were excluded. Urine dipsticks with trace or greater proteinuria were considered positive. Three groups of proteinuria were identified: no proteinuria had negative dipsticks at both examinations, transient proteinuria had a positive dipstick at one examination, and persistent proteinuria had positive dipsticks at both examinations.

Outcome Variable

Comprehensive morbidity and mortality surveillance identified all-cause mortality from 1965 through December 2010.[11]

Covariates

Baseline covariates selected as possible confounders included age, cardiovascular risk factors (body mass index, hypertension, diabetes mellitus, smoking, physical activity index, total cholesterol level and alcohol consumption), and prevalent diseases (coronary heart disease, stroke, and cancer).

Statistical Analyses

Cox regression models analyzed total mortality risk for transient and persistent proteinuria groups, adjusting for baseline covariates. Additional stratified Cox regression analyses examined subgroups with or without hypertension, diabetes mellitus, and cardiovascular diseases (defined as hypertension, diabetes, coronary heart disease, or stroke) at baseline, examining total mortality risk with positive proteinuria (transient or persistent) versus no proteinuria.

RESULTS

The final analytic sample included 6,815 subjects with urine dipstick test results from both midlife examinations. Of those, 6,297 subjects (92.4%) had no proteinuria, 433 (6.4%) had transient proteinuria, and 85 (1.2%) had persistent proteinuria. The risks of total mortality by transient, persistent, and positive proteinuria for the entire cohort and subgroups, are displayed in Table 1. In fully adjusted models, transient proteinuria was associated with a 40% increased mortality risk and persistent proteinuria was associated with over a 2-fold increased mortality risk, compared to no proteinuria. Proteinuria was associated with increased mortality risk in all subgroups with or without chronic diseases, but with higher risks in the hypertensive, diabetic and cardiovascular disease subgroups. The diabetic subgroup had the highest risk, with an 85% increase in mortality.

DISCUSSION

In this prospective observational cohort study of 6,815 Japanese-American men, proteinuria detected by urine dipstick in mid-life was independently associated with up to 39-year total mortality. In stratified analyses, positive proteinuria was independently associated with higher mortality among those with hypertension, diabetes, coronary heart disease or stroke. This longitudinal population-based study had two proteinuria measurements six years apart and an unprecedented 39-year mortality follow-up period.

Significant relationships between single dipstick proteinuria and mortality have been reported previously.[5–7] The first National Health and Nutrition Examination Study (NHANES I, n=6,000 U.S. men and women) reported that trace proteinuria or greater on urine dipstick was associated with 71% higher total mortality than no proteinuria in men.[5] The Framingham Study (n=2,586) reported that trace and 1+ or greater dipstick proteinuria were associated with 30–40% increased 17-year total mortality.[6] Dipstick proteinuria was associated with a 43% increased mortality in Italy.[7] Other population-based studies, including one arm of a cluster randomized trial,[12] a laboratory database,[13,14] and health check-ups,[15–17] may represent selected samples and lack generalizability.

This study has potential limitations. Urine dipstick results may include misclassifications,[4] although these were minimized by using urine dipstick tests from two separate occasions six years apart. Dipstick is not ideal for microalbuminuria screening, although including trace or greater proteinuria increases microalbuminuria detection.[18] We lowered the positive proteinuria threshold to trace or greater and repeated dipstick tests twice, to increase proteinuria detection. Our all-Japanese male study population may reduce generalizability. Data regarding preexisting kidney diseases, serum creatinine levels and medication use (including angiotensin converting enzyme inhibitors or angiotensin receptor blockers) were not available.

Study strengths include the large population-based and genetically homogeneous sample, nearly four decade-long follow-up period, and an extremely thorough surveillance system, with low out-migration rates and essentially complete surveillance for total mortality. We

adjusted for multiple potential confounders to assess the independent association between proteinuria and mortality.

Albuminuria may reflect widespread systemic vascular damage and endothelial disturbance with kidney involvement.[3] However, higher mortality associated with proteinuria among men without hypertension, diabetes mellitus, or renal disease may be due to occult malignancies[19] or infections.[20] Positive proteinuria should trigger further investigation, to improve health outcomes through early detection and treatment.

In summary, we found that proteinuria detected by simple urine dipstick measurement in middle-aged Japanese-American men independently predicted 39-year mortality risk. This risk was even higher among subjects with prevalent hypertension, diabetes, coronary heart disease or stroke, yet was a significant predictor of mortality even among subjects without prevalent chronic diseases. Although dipstick is a semiquantitative measure, it is inexpensive and has potential to provide quick and simple clinically useful information.

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List of abbreviations and acronyms

95%CI	95% confidence interval
HR	Hazard ratio
NHANES	National Health and Nutrition Examination Study

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Table 1

Cox regression analyses according to proteinuria status, reference = no proteinuria group.

	Age-Adjusted			Fully-Adjusted *		
	HR	95%CI	p value	HR	95%CI	p value
Entire Cohort (n=6,815)						
Transient Proteinuria vs. None	1.55	1.40–1.71	<0.001	1.40	1.26–1.55	<0.001
Persistent Proteinuria vs. None	2.50	2.01–3.10	<0.001	2.26	1.81–2.84	<0.001
<i>P for trend</i>			<0.001			<0.001
Positive Proteinuria ** vs. None	1.65	1.51–1.81	<0.001	1.49	1.36–1.64	<0.001
STRATIFIED ANALYSES – Comparing Positive Proteinuria ** to No Proteinuria						
Non-Hypertensives (n=3,206)	1.47	1.25–1.72	<0.001	1.40	1.19–1.65	<0.001
Hypertensives (n=3,608)	1.70	1.52–1.90	<0.001	1.54	1.37–1.73	<0.001
Non-Diabetics (n=5,750)	1.53	1.38–1.70	<0.001	1.40	1.25–1.56	<0.001
Diabetics (n=1,065)	1.98	1.65–2.37	<0.001	1.85	1.53–2.25	<0.001
CVD *** Not Present (n=2,621)	1.44	1.20–1.73	<0.001	1.32	1.09–1.59	0.004
CVD Present (n=4,194)	1.67	1.50–1.86	<0.001	1.56	1.40–1.74	<0.001

* Adjusted for age, body mass index, hypertension, diabetes mellitus, diabetes mellitus, pack-years smoking, physical activity index, serum cholesterol, alcohol intake, and prevalent coronary heart disease, stroke, and cancer, except for specific risk factors used for each stratified analysis.

** Positive Proteinuria = transient or persistent proteinuria (combined).

*** CVD = cardiovascular diseases at baseline, including hypertension, diabetes, coronary heart disease, or stroke.