Dipstick Proteinuria as a Screening Strategy to Identify Rapid Renal Decline

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ABSTRACT

Rapid kidney function decline (RKFD) predicts cardiovascular morbidity and mortality, but serial assessment of estimated GFR (eGFR) is not cost-effective for the general population. Here, we evaluated the predictive value of albuminuria and three thresholds of dipstick proteinuria to identify RKFD in 2,574 participants in a community-based prospective cohort study with a median of 7 years follow-up. Median change in eGFR was −0.78 ml/min per 1.73 m^2 per year; with 8.5% experiencing RKFD, defined as a >5% annual eGFR decline from baseline. Of those with RKFD, 65% advanced to a new CKD stage compared with 19% of those without RKFD. Dipstick protein ≥1 g/L was a stronger predictor of RKFD than albuminuria. Overall, 2.5% screened positive for dipstick protein ≥1 g/L at baseline; one of every 2.6 patients would have RKFD if all were followed with serial eGFR measurement. Overall, the screening strategy correctly identified progression status for 90.8% of patients, mislabeled 1.5% as RKFD, and missed 7.7% with eventual RKFD. Among those with risk factors (cardiovascular disease, age >60, diabetes, or hypertension), the probability of identifying RKFD from serial eGFR measurements increased from 13 to 44% after incorporating dipstick protein (≥1g/L threshold). In summary, inexpensive screening with urine dipstick should allow primary care physicians to follow fewer patients with serial eGFR assessment but still identify those with rapid decline of kidney function.

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Although fewer than 0.1% of Canadians have end-stage renal disease (ESRD), the economic burden of ESRD is 16 times higher per patient than the average spending for all other health-care conditions.[1] Early detection and prevention of kidney disease is the only way to prevent associated morbidity and premature mortality from cardiovascular disease (CVD) or ESRD[2]; however, kidney disease is often asymptomatic until advanced stages, making early detection unlikely in the absence of active surveillance, and this limits the opportunity for treating and delaying disease progression.[3]

Decline in kidney function may be a stronger prognostic indicator than static measures of reduced estimated GFR (eGFR). In particular, patients with rapid kidney function decline (RKFD) are at increased risk for CVD and mortality[4–7]; even among those with mildly reduced kidney function at baseline.[5,7] Dynamic eGFR assessment is necessary to identify this silently progressing, high-risk group; however, serial assessment in the general population is not cost-effective.[3,8,9] Similarly, screening for proteinuria to prevent ESRD is not cost-effective unless directed at high-risk populations.[10]

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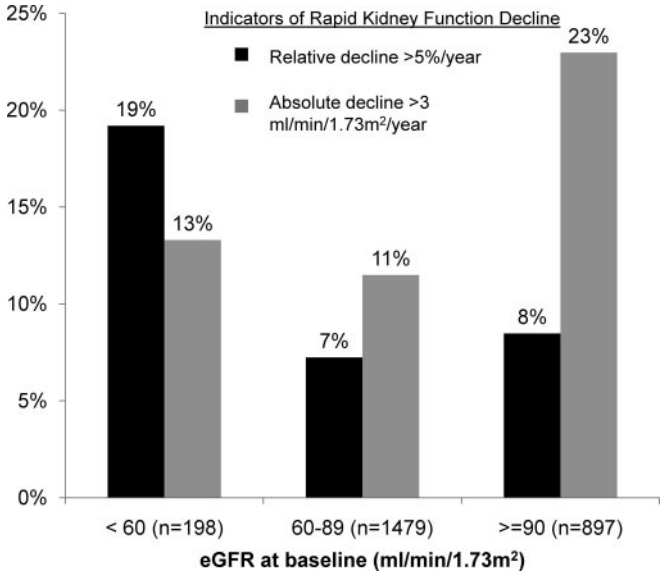

Figure 1. Indicators of rapid kidney function decline in relation to estimated GFR (eGFR) at baseline: Adults with a baseline eGFR above 90 ml/min per 1.73 m^2 were three times more likely to demonstrate an absolute decline >3 ml/min per 1.73 m^2 than a relative decline >5%.

To date, no studies have investigated the clinical utility of combining risk-factor assessment with routine screening tests to identify those at highest risk of RKFD who would most benefit from serial eGFR assessment and early intervention. In this 7-year prospective cohort study, we identify risk factors for RKFD and evaluate the ability of routine screening tests for urine protein to improve the efficiency of detecting RKFD across a broad range of eGFR values.

RESULTS

Of 2,574 adult participants with at least three annual eGFR measures, median follow-up time was 7 years with seven eGFR measurements. Participants were predominantly Caucasian (99%) and ranged in age from 18 to 92 years with 75% younger than 60 years and 25% younger than 37 years. Mean baseline eGFR was 83.6 ml/min per 1.73 m^2 (SD 18.4) with a median absolute annual change in eGFR of −0.78 ml/min per 1.73 m^2 per year (interquartile range [IQR], −2.2, 0.5) and a median percentage annual change of −0.97% (IQR, −2.60%, 0.62%). The distribution of the absolute annual change was strongly skewed to the right and susceptible to highly variable rates of annual decline in those with baseline eGFR ≥90 ml/min per 1.73 m^2. The distribution of the percentage annual change was more symmetrically balanced around the median with only three outliers (all three had baseline eGFR <60, and eGFR increased over time). When we defined RKFD as an absolute annual decline >3 ml/min per 1.73 m^2 per year, 15.6% experienced RKFD compared with 8.5% for RKFD defined as an annual percentage decline >5%. As shown in Figure 1, an absolute annual decline >3ml/min per 1.73 m^2 per year most commonly identified those with a baseline eGFR ≥90 ml/min per 1.73 m^2 (23%). Conversely, when we defined change in eGFR relative to baseline (decline >5%), RKFD was more common in those with an eGFR <60 ml/min per 1.73 m^2 (19%) and was equally distributed (~8%) across GFR categories ≥60. In addition, annual decline >5% was more strongly associated with the risk for future self-reported CVD (relative risk [RR] = 2.7, 95% confidence interval [CI] = 1.4 to 5.4, $P = 0.004$) comparyed with annual decline >3 ml/min per 1.73 m^2 (RR = 1.4, 95% CI = 0.7 to 2.6, $P = 0.35$). The remainder of the results will focus on RKFD defined as annual decline of >5%; however, a summary of the results for absolute annual decline are provided in Appendix II.

After excluding those with RKFD (8.5%), the median change in eGFR was −0.57 ml/min per 1.73 m^2 per year. Nearly two-thirds (64.7%) of those with RKFD advanced to a new stage on the basis of GFR classification compared with 19.0% of those without RKFD. Table 1 summarizes baseline characteristics, overall and by future RKFD. RKFD was more common among participants older than 60 years (16% *versus* 6%); however, there was no difference in the incidence of RKFD between men and women (9.1% *versus* 8.2%). Although RKFD was twice as common in those with an eGFR <60 *versus* ≥60 ml/min per 1.73 m^2 far more patients with eGFR ≥60 *versus* <60 presented with RKFD during follow-up ($n = 183$ *versus* 38). After adjusting for age, we found that hypertension, diabetes, CVD, obesity, and family history of diabetes were all significantly associated with increased risk for RKFD (Table 2). With the exception of obesity, which lost statistical significance in the multivariable model ($P > 0.2$), each was retained in the final, fully-adjusted clinical risk model. The greatest risk was seen among those with CVD (RR = 2.22, 95% CI = 1.57 to 3.12), followed by age ≥60, hypertension, and diabetes. Taken together, patients presenting with hypertension, diabetes, a history of CVD, or age ≥60 were nearly three times more likely to develop RKFD (RR = 2.8, 95% CI = 2.1 to 3.8). Among patients with clinical risk factors, 22% of those with a baseline eGFR <60 ml/min per 1.73 m^2 developed RKFD compared with 25% with eGFR ≥60 ml/min per 1.73 m^2.

Compared with those with normoalbuminuria, the presence of albuminuria conferred a 53% increased risk for RKFD (95% CI = 1.09 to 2.17) (Figure 2). Participants with trace levels of protein or greater had more than a two-fold increase in the risk of RKFD (95% CI = 1.51 to 3.19), which increased to 3.26 (95% CI = 1.95 to 5.45) for ≥3g/L. The left axis (frequency) in Figure 3 shows the number who screened positive for protein at baseline and the number with RKFD by screening criteria. The right axis shows the percentage of those who screened positive for protein that developed RKFD. Although more participants were identified with albuminuria ($n = 253$), far fewer developed RKFD (6%) as compared with those identified at various thresholds of dipstick protein, of which 12% with trace or above, 33% with ≥1 g/L, and 40% with ≥3 g/L of protein-developed RKFD.

Table 3 summarizes the diagnostic utility of albuminuria and/or thresholds for dipstick protein (≥trace, ≥1 g/L, or ≥3 g/L) at baseline to predict RKFD, overall and in risk subsets of

Table 1. Participant characteristics: Overall and by percent annual decline in eGFR (ml/min per 1.73 m^2 per year), 2002 to 2008

Variable	Overall (n = 2574)	Annual % decline in eGFR (ml/min per 1.73 m^2 per year)[a]		P
		≤5% (n = 2353)	>5% (n = 221)	
Study population				
years followed, median (IQR)	7 (5,7)	7 (6,7)	5 (3,7)	
number of GFR measures, median (IQR)	7 (5,7)	7 (5,7)	5 (3,7)	
male	1021 (39.7%)	928 (39.4%)	93 (42.1%)	0.47
mean age at baseline (SD)	48.4 (16.0)	47.7 (15.7)	56.0 (17.8)	<0.001
mean SBP at baseline (SD)	127.6 (19.5)	126.6 (18.7)	137.4 (24.3)	<0.001
mean DBP at baseline (SD)	74.6 (9.6)	74.4 (9.4)	76.2 (11.5)	0.02
mean baseline BMI, kg/m^2 (SD)[b]	28.6 (5.8)	28.5 (5.8)	29.0 (6.4)	0.008
eGFR (ml/min per 1.73 m^2)				
mean eGFR at baseline (SD)	84.0 (18.5)	84.2 (17.9)	81.2 (24.3)	<0.001
category of baseline eGFR				
≥90	897 (34.9%)	821 (34.9%)	76 (34.4%)	
60 to 89	1479 (57.5%)	1372 (58.3%)	107 (48.4%)	<0.001
30 to 59	188 (7.3%)	156 (6.6%)	32 (14.5%)	
<30	10 (0.4%)	4 (0.2%)	6 (2.7%)	
median annual change (IQR)	−0.78 (−2.2, 0.53)	−0.57 (−1.7, 0.7)	−5.66 (−7.7,−4.4)	
median % annual change (IQR)	−0.97 (−2.60, 0.62)	−0.7% (−2.1%, 0.8%)	−6.9% (−9.2%, −5.6%)	
Risk factors				
diabetes	366 (14.2%)	298 (12.7%)	68 (30.8)%	<0.001
cardiovascular disease	192 (7.5%)	141 (6.0%)	51 (23.1%)	<0.001
hypertension	795 (30.9%)	679 (28.9%)	116 (52.5%)	<0.001
mean age at baseline (SD)	48.4 (16.0)	47.7 (15.7)	56.0 (17.8)	<0.001
<40 years	793 (30.8%)	751 (31.9%)	42 (19.0%)	
40 to 60 years	1166 (45.3%)	1088 (46.2%)	78 (35.3%)	<0.001
>60 years	615 (23.9%)	514 (21.8%)	101 (45.7%)	
Covariates				
obesity	919 (35.7%)	816 (34.7%)	103 (46.6%)	<0.001
family history				
kidney disease	60 (2.3%)	55 (2.3%)	5 (2.3%)	0.99
hypertension	1148 (44.6%)	1044 (44.4%)	104 (47.1%)	0.48
diabetes	728 (28.3%)	647 (27.5%)	81 (36.7%)	0.005
Screening tests (at baseline)				
albuminuria[c]	253 (9.8%)	202 (8.6%)	51 (23.1%)	<0.001
dipstick protein				
>Trace	145 (5.6%)	111 (4.7%)	34 (15.4%)	<0.001
≥1 g/L	63 (2.5%)	39 (1.7%)	24 (10.9%)	<0.001
≥3 g/L	42 (1.6%)	25 (1.1%)	17 (7.7%)	<0.001

n is given as a percentage unless otherwise indicated. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated GFR; IQR, interquartile range; SBP, systolic blood pressure.

[a]Estimated using the abbreviated Modification of Diet in Renal Disease equation.[28]

[b]Missing two observations for BMI.

[c]Random albumin to creatinine ratio >2.0 mg/mmol (17 mg/g for men or >2.8 mg/mmol (25 mg/g) for women).[31,32]

the population. Overall, the probability of developing RKFD before screening was 9%. The greatest increase in the probability of RKFD came after a dipstick of ≥3 g/L. The probability of identifying RKFD from serial eGFR measurements increased from 9 to 41%; an increase in the certainty of the likelihood of disease of 7.8 after a positive test relative to a negative test. Overall, 42 (1.6%) had a dipstick protein ≥3 g/L, and if all were followed with serial eGFR measurements, one patient with RKFD would be identified for every 2.5 patients followed. The smallest increase in the probability of RKFD was seen among those with albuminuria. The probability of RKFD in this group was 20%, an increase in the certainty of the likelihood of disease of 3.2 after a positive test relative to a negative test. Overall, 63 (2.5%) had a dipstick protein value of ≥1 g/L, and if all were followed with serial eGFR measurements, one patient with RKFD would be identified for every 2.6 patients followed. On the basis of the result of a single screening test and using a criteria of ≥1 g/L of protein, 90.8% of patients were correctly identified as either RKFD or nonprogressive, 1.5% were mislabeled as RKFD, and 7.7% with eventual RKFD were missed.

Similarly, among those with risk factors (history of CVD, diabetes, or age ≥60 years), using a criteria of a dipstick protein ≥1

Table 2. Relative risk for rapid kidney function decline (>5% annual decline) among community-dwelling adults

Parameter	Age Adjusted		Fully Adjusted Clinical Risk Model[a]		
	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	*P*
Age ≥60 years	2.69	2.07, 3.50	1.73	1.28, 2.32	<0.001
Hypertension	1.90	1.43, 2.52	1.58	1.17, 2.13	0.003
Diabetes	2.11	1.56, 2.83	1.53	1.11, 2.11	0.009
Cardiovascular disease	2.62	1.87, 3.67	2.22	1.57, 3.12	<0.001
Family history					
diabetes	1.40	1.07, 1.84	1.27	0.96, 1.67	0.10
hypertension	1.20	0.92, 1.56			
kidney failure	0.89	0.37, 2.16			
Obese	1.48	1.14, 1.93			
Male gender	1.15	0.84, 1.44			

[a]Covariates were removed from the final, fully-adjusted clinical risk model if $p > 0.20$; all interactions were tested and removed at $\alpha = 0.05$.

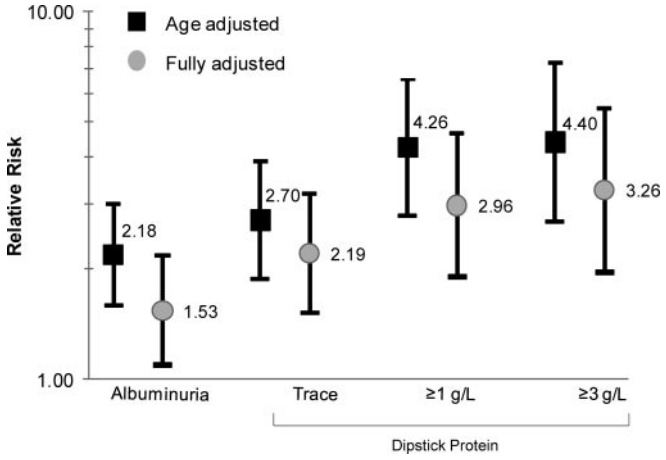

Figure 2. Dipstick protein was a stronger predictor of rapid kidney function decline (RKFD) than albuminuria. Age-adjusted and fully-adjusted relative risks for RKFD (% annual decline >5% from baseline) by screening test at baseline (albuminuria or dipstick for protein [≥trace; ≥1 g/L; ≥3 g/L]).

g/L resulted in an increase in the probability of RKFD from 13 to 44%. Although albuminuria had greater sensitivity, particularly among diabetics, a higher false-positive rate resulted in a greater number needed to follow. In fact, among patients with no preexisting risk factors, using albuminuria as a screening criteria resulted in only a slight increase in the certainty of the likelihood of disease of 1.2 after a positive test relative to a negative test, and the post-test probability of RKFD increased by <1%.

DISCUSSION

In this 7-year follow-up of a community-based cohort, dipstick proteinuria had better diagnostic utility for identifying patients at risk for RKFD than albuminuria. A dipstick for protein ≥1 g/L correctly identified 91% of those screened as either RKFD or nonprogressive. If all of the positive test results were followed with serial eGFR assessment, one patient with RKFD would be identified for every 2.6 patients followed. This decreased to 2.3 among those with CVD, diabetes, hypertension, or age ≥60 years.

Approximately 60 million individuals globally have some degree of chronic kidney disease, and early detection and prevention of kidney disease may be the only way to prevent death from CVD or ESRD.[2] Hyperfiltration after renal injury and the inability to distinguish age-related decline from pathologic renal decline pose significant barriers to early diagnosis and treatment when using static tests of kidney function. Strategies that focus on identifying progressive renal disease in those with eGFR <60 ml/min per 1.73 m^2 identify patients later in their disease, and the vast majority die of CVD before developing ESRD.[11] Our analysis focused on all adults, including those with eGFR >60 ml/min per 1.73 m^2 who may otherwise go undetected and yet are likely to experience greater therapeutic benefit if identified at an earlier stage.[12] More than 80% of those with RKFD in our community-based cohort had an eGFR >60 ml/min per 1.73 m^2. Importantly, Matsushita *et al.*[5] observed an increased risk for CVD and all-cause mortality from RKFD in those with eGFR 60 to 90 ml/min per 1.73 m^2 at baseline, and other studies of the general population show an increased risk for adverse outcomes from RKFD or proteinuria independently of baseline eGFR.[4,6,13,14] Although albuminuria has greater sensitivity at low levels and is the recommended method for monitoring proteinuria in diabetics,[15–17] we show that dipstick urinalysis, an inexpensive test that is already a common feature of primary care, has better diagnostic utility for identifying RKFD.

Despite the strong association between RKFD and adverse outcomes,[4–7] population-wide screening for eGFR is not cost-effective.[3,8,9] Our results support an alternative sequential screening strategy in which patients with dipstick protein ≥1 g/L are followed with serial eGFR assessment. Boulware *et al.*[10] demonstrated that screening for dipstick proteinuria to slow renal progression was cost-effective in high-risk populations (age >60, hypertension, and diabetes). Although cost-effectiveness was not demonstrated in low-risk groups, the major cost in their model resulted from specialist evaluation of all patients with eGFR <90. Our analysis suggests that monitoring for RKFD before specialist referral would reduce the referral rate by 80% in those without risk factors and by 56% in those with risk factors (Table 3). Moreover, the comparator group in Boulware's analysis was "no screening"; however, general practitioners routinely perform dipstick urinalysis as part of an annual physical exam. Finally, prevention of CVD morbidity should also be accounted for, because a greater

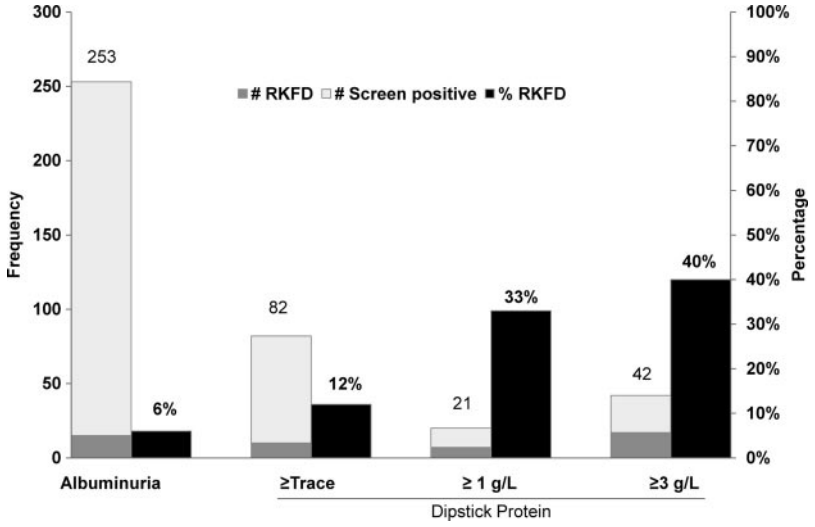

Figure 3. More adults screened positive for albuminuria than dipstick protein; however, those with dipstick protein were more likely to experience rapid kidney function decline than those with albuminuria. Number with rapid kidney function decline (#RKFD) relative to the total number who screen positive (# Screen positive) at baseline and RKFD as a percentage of those who screen positive (% RKFD); by screening test (dipstick for protein or albuminuria).

number patients with chronic kidney disease will experience CVD than ESRD.[11,18]

A standardized approach to treating patients with RKFD has yet to be developed; however, evidence that RKFD predicts CVD and mortality, even when kidney function is only mildly reduced (eGFR, 60 to 90),[5] suggests that patients with dipstick protein ≥1 g/L and eGFR <90 ml/min per 1.73 m^2 should be followed with serial eGFR assessment, and early intervention may be warranted for those with RKFD. In contrast, the meaning of RKFD at eGFR >90 ml/min per 1.73 m^2 is less clear because there is no body of evidence documenting adverse outcomes in this group.[19] Although previous research has established that proteinuria in the presence of eGFR <60 ml/min per 1.73 m^2 is a stronger risk factor for CVD and ESRD than either indicator alone,[13,20] serial eGFR assessment would provide additional information about a patient's risk trajectory. For example, in elderly patients with reduced but stable kidney function, a low eGFR (30 to 60 ml/min per 1.73 m^2) may be an indicator of age-related comorbidity rather than vascular pathology, the latter being responsive to treatment with angiotensin-receptor blockers if caused by proteinuria.[21,22] Depending on their cardiovascular risk profile and level of proteinuria, elderly patients with stable kidney function could be monitored in primary care,[23–25] whereas those with RKFD are more likely to benefit from specialist referral because they are at greater risk for adverse outcomes.[4–6] However, future research must assess the effect and cost-effectiveness of different follow-up strategies.

Although eGFR is the most readily available indicator of kidney function, there are limitations associated with its use, namely fluctuation in the assay of serum creatinine and increased measurement error associated with longitudinal tracking of eGFR. The median change in eGFR was −0.78 ml/min per 1.73 m^2 per year with 16% experiencing an absolute annual decline >3 ml/min per 1.73 m^2 per year and 9% experiencing a percentage annual decline >5%. The high variability in absolute change among those with baseline eGFR ≥90 ml/min per 1.73 m^2 made percentage change a better measure of renal decline in this general population sample.[5] In addition, percentage annual change was a stronger indicator of incident CVD than absolute change. We also conducted several sensitivity analyses to test the robustness of our findings and account for the imprecision of the Modification of Diet in Renal Disease (MDRD) GFR estimating equation at higher levels of GFR (Appendix I). Overall, dipstick proteinuria remained a stronger predictor of RKFD than albuminuria, regardless of how RKFD was defined or whether we excluded those with eGFR >90 ml/min per 1.73 m^2 or those with highly variable rates of kidney function decline.

Our study has many strengths including routine collection of serum creatinine within a nonreferred community-based sample. We measured change in kidney function across a broad age range over a 7-year time span. Our study sample included individuals with a minimum of three annual serum-creatinine measurements, and seven measures were available for more than half of the sample. Selected participants were more likely to be older or obese, with a family history of hypertension or diabetes. No differences in baseline BP, hypertension, history of CVD, or family history of kidney disease were evident; however, selected participants had a lower baseline eGFR than the original cohort. It is possible that individuals concerned with their kidney function were more likely to join the study and participate longer. Most importantly, our sample had sufficient variability in both initial GFR and change over time to allow the estimation of risk of RKFD across the spectrum of eGFR categories.

CONCLUSION

Dipstick urinalysis, an inexpensive test that is already a common feature of primary care, has better diagnostic utility for identifying patients at risk for RKFD than albuminuria. Screening for dipstick proteinuria ≥1 g/L in patients with or without risk factors would allow clinicians to follow fewer patients with serial eGFR assessment to identify those with RKFD. This novel strategy, although not identifying all patients with silent RKFD, addresses the shortcomings of many prior studies by changing the focus from static eGFR assessment among those with an eGFR below 60 ml/min per 1.73 m^2

Table 3. Comparison of the diagnostic utility of thresholds for dipstick protein and albuminuria at baseline to identify patients with future rapid kidney function decline: Overall and by risk subsets of the population

	n	%	Pretest Probability of RKFD	Screen Positive (%)	False-Positive Rate	LR+/LR−	Posttest probability of RKFD	NNTS	NNTF
Overall	2574	100%	0.09						
albuminuria[a]	253			9.8	8.9	3.2	0.20	10.2	5
dipstick protein									
≥trace	145			5.6	4.7	3.7	0.23	17.8	4.3
≥1 g/L	63			2.5	1.7	7.2	0.38	40.9	2.6
≥3 g/L	42			1.6	1.1	7.8	0.41	61.3	2.5
No risk factors[b]	1393	54%	0.05						
albuminuria[b]	55			4	3.9	1.2	0.05	25.3	18.3
dipstick protein									
≥Trace	54			3.9	3.7	2.2	0.09	25.8	10.8
≥1 g/L	15			1.1	0.9	5.4	0.20	92.9	5
≥3 g/L	11			0.8	0.7	4.7	0.18	126.6	5.5
With risk factors[a]	1181	46%	0.13						
albuminuria[b]	198			16.8	14.7	2.6	0.24	6	4.1
dipstick protein									
≥Trace	91			7.7	6.1	3.5	0.32	13	3.1
≥1 g/L	48			4.1	2.6	5.7	0.44	24.6	2.3
≥3 g/L	31			2.6	1.6	6.7	0.48	38.1	2.1
Diabetes	366	26%	0.19						
albuminuria[b]	107			29.2	24.5	3.1	0.32	3.4	3.1
dipstick protein									
≥Trace	44			12.0	8.7	3.8	0.41	8.3	2.4
≥1 g/L	33			9.0	5.4	5.9	0.52	11.1	1.9
≥3 g/L	21			5.7	3.4	5.6	0.52	17.4	1.9
Other risks[c]	815	59%	0.11						
albuminuria[b]	0			11.2	10.6	1.6	0.15	9.0	6.5
dipstick protein									
≥Trace	0			5.8	5.0	2.7	0.23	17.3	4.3
≥1 g/L	0			1.8	1.5	3.0	0.27	54.3	3.8
≥3 g/L	724			1.2	0.8	5.6	0.40	81.5	2.5

LR+/LR−, ratio of positive to negative likelihood ratios; NNTF, number of patients needed to follow with serial serum-creatinine measurements to identify one case of RKFD (the inverse of the prevalence of RKFD among screen positive); NNTS, number of patients needed to screen to identify one positive result (the inverse of the prevalence of a positive screening result); RKFD, rapid kidney function decline (% annual eGFR decline >5%).

[a]Random albumin to creatinine ratio >2.0 mg/mmol (17 mg/g for men or >2.8 mg/mmol (25 mg/g) for women).[25,26]

[b]Age >60 years, cardiovascular disease, hypertension, or diabetes.

[c]Age >60 years, cardiovascular disease, or hypertension.

to dynamic assessment of those with an eGFR both above and below 60 ml/min per 1.73 m^2. This strategy will enable earlier identification of many patients with RKFD in the general population, of whom the large majority have eGFR above 60 ml/min per 1.73 m^2. At the population level, this screening strategy may enable more appropriate targeting of resources. However, future research must assess the effect and cost-effectiveness of different follow-up strategies in independent cohorts.

CONCISE METHODS

Participants and Design

Data for this analysis were obtained from The Walkerton Health Study (2002 to 2008), a prospective cohort study designed to evaluate the long-term health sequelae after exposure to bacterially contaminated water.[26] The study sample has previously been shown to be representative of the target population, with a slight over-representation of women and a slight under-representation of the very elderly.[27] Ethics approval was obtained from the University of Western Ontario's Research Ethics Board for Health Sciences. Of 3,371 participants ≥18 years, we excluded 797, including those who developed hemolytic uremic syndrome as a result of the outbreak ($n = 2$) and those with fewer than three annual eGFR measurements ($n = 791$) or missing baseline data for random urine protein ($n = 4$).

Measures

Participants completed a baseline assessment that included questions on risk factors, family history, and doctor-diagnosed health conditions (following the format of the U.S. Third National Health and Nutrition Examination Survey). We measured height, weight, and BP using standardized protocols, and blood and urine samples were collected annually.[26] We used a urine dipstick for protein (Bayer 8SG Multistix) to measure protein from a random spot urine sample, and the IMAGE Beckman Coulter immunoassay (Fullerton, CA) to mea-

sure the albumin:creatinine ratio. Serum creatinine was measured by the modified kinetic method of JAFFE using a Vitros 950 autoanalyzer, with an interassay coefficient of 4% (reference normal range, 59 to 117 μmol/L for men and 51 to 95 μmol/L for women). We calculated eGFR using the abbreviated MDRD equation.[28]

To calculate the rate of change in eGFR over time, we fitted an ordinary least-squares regression line to all eGFR measures for each participant. The slope of the regression line describes the rate of change in kidney function over time. On the basis of previous research, we defined RKFD as both an absolute annual decline >3 ml/min per 1.73 m^2 per year[4] and as a percentage annual decline >5% (slope/baseline eGFR*100).[5]

We defined CVD as a self-reported, doctor-diagnosed heart attack, stroke, or congestive heart failure and recorded the date of diagnosis. We defined diabetes mellitus by the current diagnostic criteria[29] on the basis of random or fasting plasma glucose, or 2-hour oral glucose tolerance test or current medication (oral hypoglycaemic agents or insulin). We classified participants taking anti-hypertensive medication or presenting with a systolic/diastolic BP ≥140/90 mmHg (or ≥130/80 mmHg in the presence of diabetes or eGFR <60 ml/min per 1.73 m^2)[30] as hypertensive. We examined two random urine screening tests for proteinuria obtained at baseline: the dipstick for protein (≥trace, ≥1 g/L, and ≥3 g/L) and albuminuria (albumin:creatinine ratio >2.0 mg/mmol for men or >2.8 mg/mmol for women).[31,32] We chose additional covariates on the basis of their biologic plausibility or prior studies, including: male gender, obesity (body mass index of ≥30 kg/m^2), and family history of diabetes, kidney disease, or hypertension. We distinguished between recognized clinical risk factors for RKFD (age ≥60, CVD, diabetes, and hypertension) and screening tests for urine protein to improve prediction of RKFD.

Analyses

We used SAS 9.2 (SAS Institute, Inc., Cary, NC) for all analyses and summarized normally distributed data by the mean and SD and skewed distributions by the median and IQR. We tested the associations between RKFD and baseline characteristics and screening tests using *t* tests and χ^2 tests as appropriate. We used a log-binomial model to estimate the adjusted RR for RKFD and tested covariates for inclusion at $\alpha = 0.20$ and interactions among clinical risk factors, as well as interactions between clinical risk factors and baseline eGFR <60 at $\alpha = 0.05$. We estimated the adjusted RR for RKFD at three separate cut-points for dipstick protein (≥trace, ≥1 g/L, and ≥3 g/L) and albuminuria at baseline by adding them separately to the clinical risk model. We assessed the diagnostic utility of thresholds for dipstick protein and albuminuria to identify RKFD, both overall and within high-risk subgroups (definitions in Appendix II).

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All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (*1*) no authors have received support from any companies for the submitted work; (*2*) no authors have any relationships with any companies that might have an interest in the submitted work in the previous 3 years; (*3*) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (*4*) no authors have nonfinancial interests that may be relevant to the submitted work.

DISCLOSURES

None.

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See related editorial, "Screening for Proteinuria: A Tool for Predicting Rapid Declines in Kidney Function?," on pages 1580–1583.

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