ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

September 2011 | Vol. 3, Number 9

A Simple Urine Test Detects Rapid Kidney Function Decline

By Tracy Hampton

A simple and inexpensive urine test that can be routinely performed in family physicians' offices can help identify individuals who are silently experiencing rapid kidney function decline (RKFD), according to new research. The test could help save lives because RKFD predicts cardiovascular morbidity and mortality, but serial assessment of kidney function by measuring estimated GFR (eGFR) is not cost effective for the general population.

"Our new strategy using a simple urine dipstick allows clinicians to follow fewer patients with serial eGFR assessments to identify those with rapid kidney function decline," said William Clark, MD, of the University of Western Ontario and London Health Sciences Centre, in London, Ontario, Canada, who was the lead author of the *Journal of the American Society of Nephrology (JASN)* study. "This strategy enables earlier identification of many patients with rapid kidney function decline in the general population and will potentially provide an opportunity to introduce therapy to reduce cardiovascular mortality and end stage kidney failure in this asymptomatic subgroup," he added.

Detecting kidney decline

For the approximately 60 million people globally who have chronic kidney disease, early detection and treatment are crucial for preventing kidney failure and cardiovascular complications. Unfortunately, individuals with chronic kidney disease often do not experience symptoms until later stages of the disease. In particular, patients with RKFD are at increased risk for cardiovascular disease and mortality, even when they have only mildly reduced kidney function at baseline.

Although serial monitoring of kidney function in the general population would likely catch such silently progressing disease early, it is too expensive. Simi-

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New Ways to Diagnose and Treat Diabetic Nephropathy Is Topic of Joint Symposium

By Cathy Yarbrough

With "disturbing news about diabetic nephropathy" as a backdrop, Lori M. Laffel, MD, MPH, co-chaired the first joint symposium of ASN and the American Diabetes Association (ADA) on June 27 as part of ADA's 71st annual meeting in San Diego. "Despite an increase in the use of pharmacological therapies, the prevalence of diabetic nephropathy (DN) has not decreased," said Laffel, of the Joslin Diabetes Center.

Laffel was referring to findings published in the June *Journal of the American Medical Association (JAMA)*, "Temporal Trends in the Prevalence of Diabetic Kidney Disease in the United States," based on data from the National Health and Nutrition Examination Survey.

The proportion of diabetic patients taking glucose-lowering medications climbed from 56.2 percent in 1988–1994 to 74.2 percent in 2005–2008, according to the *JAMA* article, and the use of renin-angiotensin-aldosterone system inhibitors soared from 11.2 percent to 40.6 percent during those same time periods. However,

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larly, screening for proteinuria to prevent ESRD is not cost effective unless it is directed at high-risk populations.

To date, no studies have investigated the clinical utility of combining risk-factor assessment with routine screening tests to identify those at highest risk for RKFD who would benefit the most from serial eGFR assessment and early intervention.

To conduct such an investigation, Clark and his colleagues designed a prospective cohort study to identify the risk factors for RKFD and to evaluate the ability of routine screening tests for urine protein to improve the efficiency of detecting the condition across a broad range of eGFR values.

A simple test

The investigators monitored 2574 participants in a community-based clinic for an average of 7 years. They found that dipstick proteinuria (a urinary protein concentration of ≥1 g/L) had better diagnostic utility for identifying patients at risk for RKFD than did albuminuria (albumin:creatinine ratio of >2.0 mg/mmol if male or >2.8 mg/mmol if female). Although more participants were identified with albuminuria (n = 253), fewer developed RKFD (6 percent) in comparison with those identified at various thresholds of dipstick protein. Among the participants who developed RKFD,12 percent had trace or above protein; 33 percent, ≥1 g/L protein; and 40 percent, ≥3 g/L protein.

Overall, 2.5 percent of participants in the study had a urinary protein concentration of ≥1 g/L at the start of the study. If all of them were followed up with serial monitoring of kidney function, one case of RKFD would be identified for every 2.6 patients who were monitored. This decreased to 2.3 among those with cardiovascular disease, diabetes, or hypertension or who were 60 or older.

The test correctly identified whether or not individuals had RKFD in 90.8 percent of participants, mislabeled 1.5 percent as having the condition, and missed 7.7 percent who were later identified as having the condition. Among those with cardiovascular disease, diabetes, or hypertension or who were age 60 or older, the probability of identifying RKFD from serial kidney function measurements increased from 13 percent to 44 percent after the incorporation of a positive dipstick test result. Although albuminuria had greater sensitivity, particularly among persons with diabetes, a higher false-positive rate resulted in a greater number to follow up.

"This novel strategy, although not identifying all with RKFD, addresses the shortcomings of many prior studies by changing the focus from static eGFR assessment among those with eGFR below 60 mL/min per 1.73 m^2 to dynamic assessment of those with eGFR above and below 60 mL/min per 1.73 m^2," Clark said.

He added that strategies that focus on identifying progressive renal disease in individuals with eGFR below 60 mL/min per 1.73 m^2 identify patients later in their disease. This analysis focused on all adults, including those with eGFR above 60 mL/min per 1.73 m^2, whose conditions may otherwise go undetected and yet are likely to experience greater therapeutic benefit if the disorder is identified at an earlier stage. More than 80 percent of those with RKFD in the study cohort had an eGFR above 60 mL/min per 1.73 m^2.

"The paper by Clark et al is a major step forward in the ongoing search for a practical and universal Renal Risk Score that can be used to predict the likelihood of progressive renal failure and eventual end stage renal disease in subjects within the general population, in a fashion similar to the Framingham Risk Score for cardiovascular risk assessment," said Richard Glassock, MD, who was not involved with the research and is professor emeritus at the David Geffen School of Medicine at UCLA in Los Angeles.

Next steps

The techniques described in this study should not be difficult to incorporate into the clinic, but Hiddo Lambers Heerspink, PharmD, PhD, of the University Medical Center Groningen in the Netherlands, noted that confirmation of the approach in other independent cohorts is needed before the strategy can be implemented.

"How and whom to screen for kidney disease remains an unanswered question,"

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ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-659-0599

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly. Application to mail as Periodicals Postage Pending at Washington, DC, and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

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said Catherine Clase, MB, FRCPC, of McMaster University in Hamilton, Ontario, Canada. "There is now little doubt that further research into screening strategies for kidney disease should, as the authors suggest, incorporate both measurement of urine protein and dynamic assessment of clearance. Dipstick proteinuria looks very attractive as a metric for assessment of proteinuria."

Early treatment may be warranted for those who are found to have RKFD as determined by the techniques in this study, but future research is needed to assess the impact and cost effectiveness of different follow-up strategies.

"The next and much more difficult step will be show that early intervention in subjects with high Renal Risk Scores but without marked proteinuria or moderately depressed eGFR actually prevents progression and avoids end-stage renal disease," said Glassock.

Joint Symposium

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during these two periods, the prevalence of impaired GFR increased from 14.9 percent to 17.7 percent. Although impaired albuminuria declined from 27.3 percent to 23.7 percent, this decrease was not statistically significant, according to the authors of the *JAMA* article.

Titled "New Concepts in Diagnosing and Treating Diabetic Nephropathy," the first joint symposium was targeted to endocrinologists and other ADA conference attendees. The second joint symposium is slated to occur at ASN's Kidney Week 2011, Nov. 8–13, in Philadelphia.

"We [nephrologists] spend a lot of time taking care of patients with diabetes, since it is the leading cause of chronic kidney disease and end stage kidney disease," said symposium co-chair and ASN past president Sharon Anderson, MD. "So it behooves us as nephrologists to stay current on diabetes treatments."

ASN president Joseph V. Bonventre, MD, PhD, spoke about the role of renal proximal tubule injury and dysfunction in the pathophysiology of DN. Bonventre, of Harvard Medical School, was one of the four symposium speakers.

"Specific proximal tubular injury leads to interstitial fibrosis and glomerulosclerosis," he said. "It may be that the kidney tubules are the primary place where diabetes has its earliest actions."

A potential sensitive and specific biomarker for early tubular injury is the transmembrane glycoprotein kidney injury molecule-1 (KIM-1), which Bonventre's laboratory cloned and characterized. Expressed only by proximal tubule cells, KIM-1 is undetectable in normal kidneys. With acute kidney injury, the mRNA and the protein are markedly upregulated.

In mice models, long-term expression of KIM-1 leads to kidney failure, and replacement of normal KIM-1 with a mutated form results in a molecule that fails to uptake oxidized lipids and glycation end products, said Bonventre. Citing unpublished research from his laboratory, he noted that high ambient glucose enhances KIM-1 expression in renal epithelial cells.

In a February 2011 *Kidney International* article, Bonventre and colleagues reported that low urinary levels of KIM-1 and the lysosomal enzyme N-acetyl-beta-D-glucosaminidase (NAG) are associated with regression of microalbuminuria (MA) in patients with type 1 diabetes (T1D) who were monitored for two years. MA regression occurred independently of glycemic control, blood pressure, or treatment with angiotensin converting enzyme inhibitors.

Bonventre and colleagues also reported that significantly elevated urinary levels of KIM-1 and NAG characterized patients with T1D and MA in comparison with diabetic patients with normoalbuminuria and with healthy control individuals without diabetes. These and other studies suggest that KIM-1 may serve not only as a therapeutic target for drug development but also as the basis of an early diagnosis test for DN.

Symposium speaker Bruce A. Perkins, MD, MPH, addressed predictive biomarkers of early DN beyond MA.

"Recent studies have shown us that microalbuminuria on its own is not the perfect predictor of who will develop advanced kidney disease, and we need to get beyond the idea of relying so much on microalbuminuria," he said.

In the recent studies, elevated urinary albumin excretion regressed to normoalbuminuria in a majority of T1D patients. In only a minority of T1D patients did MA lead to proteinuria, said Perkins, of the University of Toronto.

"What we and others have learned is that the old notion that people don't start to lose renal function until they have proteinuria appears to have been false," he pointed out. In about one third of T1D patients, GFR loss can begin at the onset of microalbuminuria, well before proteinuria appears. "End stage renal loss can occur before proteinuria," Perkins noted, referring to the Joslin Diabetes Center's findings of renal function decline in T1D patients with normal albumin excretion.

As a potential biomarker for early GFR loss, Bruce proposed serial measurement of serum cystatin C, a cysteine protease inhibitor that is freely filtered by the renal glomeruli and metabolized by the proximal tubule.

In an April 2011 issue of *JAMA*, researchers reported that combining creatinine-based estimated GFR and urine albumin-to-creatinine ratio with cystatin C was associated with improved prediction of end stage kidney disease and all-cause death. Cystatin C and albuminuria were both strongly and independently associated with all-cause death among patients