Higher levels of muscle mass contribute to higher quality of life for dialysis patients and could partially explain the “obesity paradox,” in which dialysis patients with a higher body mass index (BMI) have greater survival times than those with a lower BMI, according to a new study. The longer survival of heavier patients has long confused researchers because obese dialysis patients generally have lower levels of physical function, and better physical function is also associated with better survival as well as better quality of life.

A new study in the Clinical Journal of the American Society of Nephrology used MRIs and other measures to better define body composition to tease out the relative effects of fat and muscle in these patients. Greater muscle mass was associated with better physical function among patients with similar BMIs. The results highlight the limitations of relying on BMI alone and imply that patients could benefit from interventions to increase muscle mass.

The study involved 105 maintenance hemodialysis patients at the University of Utah and at Vanderbilt University Medical Center. BMI is an easy but crude measure of body composition that does not differentiate how much of a person’s weight is due to fat compared to muscle. So in addition to the patients’ BMI, the researchers measured their waist circumference. To get a better idea of each patient’s personal make-up, they used MRI to gauge the mid-thigh muscle level and amount of intra-abdominal fat. They assessed physical function by testing how far the patients could walk in six minutes and quality of life through questionnaires about physical function and mental health status. The patients were tested at the start of the study, after six months, and at the end of the study.

The Centers for Medicare & Medicaid Services (CMS) has announced a new—and likely its last—request for applications (RFA) for the ESRD Seamless Care Organizations (ESCOs).

If the RFA does not yield the expected 10 to 15 unique ESCO participants, CMS said it will consider scrapping the program. CMS emphasized that it reserves the right to terminate any model if it is not achieving the goals of the initiative. In its announcement, CMS stated that while it is “committed to improving care for beneficiaries with ESRD, the Agency reserves the right to decide not to move forward with the [Comprehensive ESRD Care] Model for any reason, as is true for all models.”

Yet it is not all bad news for the future of the ESCO program. CMS has made vast improvements in this latest RFA, including changes to address rebasing concerns in years 4 and 5, and releasing proposed quality measures that would assess program participants’ performance.

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Continued from page 1
and after 12 months.

The patients with higher BMI, greater waist circumference, and more abdomi- nal fat had poorer scores on the walking test as well as worse scores on the quality-of-life questionnaires. Underweight pa- tients also performed worse than patients with a normal BMI, a detail that could also reflect the effects of muscle mass.

“Because survival rates are better among dialysis patients with higher BMI, some people have argued that obesity is good in dialysis patients. This study is showing that it’s much more nuanced than that,” said lead study author Srinivasan Beddhu, MD, of the University of Utah School of Medicine in Salt Lake City. “Higher fat mass is associated with worse physical function, and more mus- cle mass is associated with better physi- cal function. So from the point of view of physical function and quality of life, obesity is not good for dialysis patients.”

Beddhu told *ASN Kidney News* that the relationship between mortality and BMI is complicated, with somewhat higher BMIs having a survival advantage even in the general population. In the U-shaped as- sociation, it seems bad to have either too much or too little fat. In the dialysis popu- lation, the curve shifts, with even higher levels of BMI having lower death risks. A higher BMI also seems to confer a survival advantage in patients with other chronic conditions such as heart failure and lung disease. “But that does not mean that fat is better than muscle,” Beddhu said.

“This is a well-designed study where they have made careful measurements to try to separate out the influences of fat and muscle,” said Kirsten Johansen, MD, professor of medicine at the University of California, San Francisco, School of Medicine and director of dialysis at the San Francisco VA Medical Center, who was not involved in the study. Johansen said that the findings do not surprise her, but add important new data about the roles of fat and muscle.

“I’ve become convinced that, from a purely survival point of view, having a re- serve of fat is good in case you get sick. But it isn’t good for physical function,” Johansen said. “I get nervous when peo- ple say patients who have higher body fat have better outcomes, so we should just let them be like that. These patients have really low levels of physical functioning and physical activity, so something that is having a negative impact on that may be having an impact on their quality of life, even if it is not negatively associated with survival. These data are highlighting once again that survival isn’t everything.”

The study’s findings are consistent with other recent reports looking at the role of muscle mass in dialysis patients, according to Kamyrat Kalantar-Zadeh, MD, MPH, PhD, chief of the division of nephrology and hypertension and professor of medicine at the University of California Irvine School of Medicine. Kalantar-Zadeh was the lead author of a similar study of almost 800 maintenance hemodialysis patients published in the *Clinical Journal of the American Society of Nephrology* in 2010. That study used mid-arm muscle circumference as a sur- rogate for lean body mass and triceps skinfold as a surrogate for fat mass. The study found that patients with more mid- arm muscle not only ranked higher on a mental health, quality-of-life scale but also had greater five-year survival rates. That finding of greater survival adds im- portant information, considering that the study by Beddhu and colleagues was cross-sectional, giving a snapshot in time of the association of the patients’ baseline levels with better quality of life.

Kalantar-Zadeh said that more stud- ies are needed to go beyond associations and establish causation. “Dialysis patients have very high mortality and they have very poor quality of life. We need more studies to show whether doing something to increase muscle mass improves the out- comes in physical function and quality of life. If these associations are causal, inter- ventions to increase muscle mass may im- prove patient outcomes,” he said.

Johansen agreed that “we need longi- tudinal studies and intervention studies to see what happens if we have patients lose weight and build up muscle. Can we improve patients’ functioning by doing these things?”

Beddhu echoed this assessment: “Be- cause this study shows that higher mus- cle mass is associated with better physi- cal function and quality of life in dialysis patients, intervention studies are needed to increase physical activity that decrease fat mass and increase muscle mass are likely to improve physical function, quality of life, and survival in dialysis patients. Such interventions need to be tested in clinical trials.”

**ESCOs**
Continued from page 1

to reduce duplicative services and expen- ditures, the ACO would consolidate all aspects of care for patients with end stage renal disease (ESRD).

According to CMS, the initiative will identify, test, and evaluate new ways to optimize the quality of care for Medicare beneficiaries with ESRD. To do so, CMS will partner with health care providers and suppliers to test the effectiveness of a new payment- and service-delivery model with the goal of providing beneficiaries patient- centered, high-quality care resulting in improved outcomes and overall Medicare savings.

**Positive changes to the ESCO application process**

ASN believes that CMS’s revised RFA was a step in the right direction and may en- tice organizations to participate in the pro- gram. The new RFA eliminates its original concept of reimbursing the program in years 4 and 5. This would have effectively penalized the highest performing ESCOs. This is a major change that will make the program more attractive to participants who are investing in costly resources and activities that will deliver better, higher-value care—the goal of the ESCO pro- gram.

Second, CMS said that allowing aggreg- ation of beneficiary numbers and financial benchmarking information among smaller, non-large dialysis organization (LDO) providers is a positive change that might induce smaller providers to participate.

Finally, removing the requirement that nephrologists must be independent enti- ties will likely make it possible for more nephrologists to consider becoming an ESCO-participant owner. Consequently, a nephrologist could be employed full or part time by another entity and still take an ownership share in the ESCO.

**Outstanding challenges**

Although CMS has made significant changes to attract greater participation, some are still concerned these changes may not be enough. Challenges to the program still remain. For instance, no end points have been established regarding what suc- cess will look like or how ESCOs will be judged as a success or a failure. The pro- gram is fundamentally an experiment, but

in the scientific world one would never start a trial without first determining the end points being aimed for and what would define success.

Another major concern is how the ESCO program will incentivize kidney transplantation, one of the program’s stated goals. Financial incentives in the current RFA do not seem to be aligned to promote transplantation, and CMS has not articulated any strategies to rectify this.

The proposed technical expert panel (TEP) measure recommendations put forth were either not tested for dialysis pa- tients or were recycled from general ACOs, not accounting for protocols that ESCOs would already be following. By making the proposed measures nonspecific to an ESCO population, CMS is increasing the administrative burden while not increas- ing patient quality. If the care organization is targeting a very specific population, the metrics should be as specific as possible to fit the unique needs of that population in order to optimize patient quality of life, satisfaction, and outcomes.

In addition, CMS does not take into account that ESCOs are incentivized to reduce expensive hospital-based care. This means that metrics designed to reduce hospitalizations and other expensive care causes to work within the community to final- ize measures that fit the ESCO patient populations, and maintains that, if im- plemented appropriately, they could save costs while providing the highest care for patients.

The deadlines to apply for the ESCO program are June 23, 2014, for LDOs and September 14, 2014, for non-LDOs. CMS stated that the letters of intent will be used only for planning purposes and will not be binding. Applicants may access the application portal at [https://innova- tiongov.force.com/rfa](https://innovationgov.force.com/rfa).
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INDICATION and Important Limitations

• SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

• Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA. It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients.

IMPORTANT SAFETY INFORMATION

SAMSCA should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriplegia, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

Contraindications: Urgent need to raise serum sodium acutely, inability of the patient to sense or appropriately respond to thirst, hypovolemic hyponatremia, concomitant use of strong CYP 3A inhibitors, anuric patients, and hypersensitivity (e.g. anaphylactic shock, rash generalized) to tolvaptan or its components.

Warnings and Precautions:

• Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium or develop neurologic sequelae, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction should generally be avoided during the first 24 hours.

• SAMSCA can cause serious and potentially fatal liver injury. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover may be impaired. Limit duration of therapy with SAMSCA to 30 days.

• Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted. In patients who develop medically significant signs or symptoms of hypovolemia, discontinuation is recommended.

• Co-administration with hypertonic saline is not recommended.

• Avoid concomitant use with: CYP 3A inhibitors and CYP 3A inducers. The dose of SAMSCA may have to be reduced if co-administered with P-gp inhibitors.

• Monitor serum potassium levels in patients with a serum potassium >5 mEq/L and in patients receiving drugs known to increase serum potassium levels.

Adverse Reactions - The most common adverse reactions (SAMSCA incidence ≥5% more than placebo, respectively): thirst (16% vs 5%), dry mouth (13% vs 4%), asthenia (9% vs 4%), constipation (7% vs 2%), pollakuria or polyuria (11% vs 3%) and hyperglycemia (6% vs 1%).

Gastrointestinal Bleeding in Patients with Cirrhosis – In patients with cirrhosis in the hyponatremia trials, GI bleeding was reported in 10% of tolvaptan-treated patients vs 2% for placebo.

Please see Brief Summary of FULL PRESCRIBING INFORMATION, including Boxed WARNING, on following page.
SAMSCA® (tolvaptan) tablets for oral use

SAFETY AND EFFICACY

SAMSCA is contraindicated in patients with symptomatic hyponatremia and in those with severe fluid retention due to congestive heart failure or kidney disease who require diuretic therapy. Use of SAMSCA therapy requires close management of vital signs, fluid balance and electrolytes. Fluid restriction during therapy with SAMSCA may increase the risk of symptomatic hyponatremia. SAMSCA has not been studied in a setting of urgent need to raise serum sodium rapidly. Because clinical trials are conducted under widely varying conditions, adverse reactions rates cannot be compared directly to those from another trial and may not reflect the rates observed in clinical practice.

INDICATIONS AND USAGE: SAMSCA is indicated for the treatment of clinically significant hyponatremic patients (serum sodium <125 mEq/L) who are dehydrated or at risk for dehydration, or those with moderate to severe hepatic cirrhosis who are symptomatic due to hyponatremia. SAMSCA is not indicated for the treatment of hyponatremic patients at a rate at least 2% greater than placebo: mortality (12% tolvaptan, 38% placebo), nausea (21% tolvaptan, 9% placebo), thirst (12% tolvaptan, 2% placebo), dry mouth (7% tolvaptan, 2% placebo) and polyuria or pollakiuria (4% tolvaptan, 1% placebo).

CONTRAINDICATIONS: SAMSCA is contraindicated in the following conditions:

- Known or suspected demyelinating syndrome
- The presence of fluid retention due to congestive heart failure or kidney disease who require diuretic therapy
- Severe fluid retention, including those with severe malnutrition, atrophic or advanced liver disease, slower rates of correction may be advisable.
- Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those with severe fluid retention, including those with severe malnutrition, atrophic or advanced liver disease, slower rates of correction may be advisable.
- Severe fluid retention due to congestive heart failure or kidney disease requiring diuretic therapy
- SAMSCA is contraindicated in patients with symptomatic hyponatremia (e.g., anaphylactic shock, rash) generalised to the systemic manifestation of the adverse event (see Adverse Reactions). (5.2)

WARNINGS AND PRECAUTIONS:

- Tolvaptan can cause severe hypovolemia, which may lead to severe dehydration and hypovolemia, and serious adverse events in patients with a serum sodium <130 mEq/L. (See Dose and Administration (2.3) and Warnings and Precautions (5.5).) P-gp Inhibitors: Co-administration of SAMSCA with strong P-gp inhibitors such as clarithromycin, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, and lopinavir/ritonavir can increase the plasma concentrations of tolvaptan and, therefore, the risk of symptomatic hyponatremia. (5.4)

- Digoxin is a P-gp substrate. Co-administration of SAMSCA with digoxin increased vW Factor Antigen or Factor VIII activity. It is not recommended to co-administer digoxin with SAMSCA. (5.5)

- The efficacy of SAMSCA may be reduced in patients concurrently treated with beta-blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics. (5.8)

- Moderate and severe hepatic impairment do not affect exposure to tolvaptan to a clinically significant extent. (5.9)

- Geriatric Use: Of the total number of hyponatremic subjects treated with SAMSCA in clinical studies, 42% were 65 and over, while 12% were 75 and over. No overall differences in safety or efficacy were observed between these and younger subjects, and other reported clinical experience has not identified differences in responses between older and younger patients. However, increasing age has no effect on tolvaptan plasma concentrations. (5.10)

- Severe fluid retention, including those with severe malnutrition, atrophic or advanced liver disease, slower rates of correction may be advisable. (5.12)

- Use in Patients with Congestive Heart Failure: The exposure to tolvaptan in patients with congestive heart failure is not critically ill is not known. (5.13)

- OVERDOSAGE: Single doses up to 400 mg and multiple doses up to 360 mg once daily for 5 days have been well tolerated in clinical trials. In a study of 12 patients treated with 400 mg of tolvaptan once daily for 4 days alone, no toxicity was observed. (5.14)

- PATIENT COUNSELING INFORMATION: As a part of patient counseling, healthcare providers must review the SAMSCA label for detailed information on the use of SAMSCA, including the possible serious adverse reactions (≥5% incidence) and how to manage them. (6)

- Other Drugs Affecting Exposure to Tolvaptan: The concomitant use of SAMSCA with CYP 3A inhibitors may lead to a marked increase in tolvaptan concentrations (see Dose and Administration (2.3), Drug Interactions (7.5)).

- Pregnancy: Pregnancy Category C. There are no adequate and well controlled studies of SAMSCA use in pregnant women. In women who may become pregnant, use SAMSCA only if the potential benefit justifies the potential risk to the fetus. (8.1)

- Nursing Mothers: There is no information on the effects of tolvaptan on breast-feeding. Because many drugs are excreted in human milk, caution should be exercised when SAMSCA is administered to a nursing woman. (8.3)

- Laboratory Tests: The effect of SAMSCA on laboratory tests in labor and delivery is unknown. (8.4)

- Use in Specific Populations: There is no adequate and well controlled studies of SAMSCA use in neonates. (8.5)

- Idaho. Use of SAMSCA in labor and delivery is unknown. (8.6)
A biomarker is defined as a characteristic that can be objectively measured and evaluated as an indicator of normal biologic or pathogenic processes of pharmacological responses to a therapeutic intervention (1). Examples of biomarkers are proteins; lipids; microRNAs; genomic, metabolomic, or proteomic patterns; imaging determinations; electrical signals; and cells present on a urinary analysis. This issue will focus primarily on serum and urine proteins. A partial list of candidate markers for kidney injury is presented in Figure 1 with corresponding sites of injury along the nephron.

Legacy kidney biomarkers include serum creatinine ($\text{sCr}$), blood urea nitrogen (BUN), urinary albumin/protein and volume excretion. However, $\text{sCr}$ or BUN cannot distinguish injury from hemodynamic changes in the kidney that lead to appropriate changes in glomerular filtration rate (GFR), particularly when the changes are acute. Furthermore, $\text{sCr}$ or BUN cannot change quickly enough with injury since individuals with normal renal function have a functional reserve that is brought into play in response to nephron injury. Other nephrons increase their function so that $\text{sCr}$ and BUN may not move out of the “normal range” until there is a great deal of injury and potentially irreversible loss of nephrons. Thus GFR, whether measured by $\text{sCr}$ or by more direct methods such as iothexol clearance, is a measure of function of the kidney which is clearly important but which may not move in sync with injury under all circumstances.

Having a biomarker that directly reflects injury, and is easily measured from a body fluid that is easily obtained, such as blood or urine, would change the paradigm to facilitate direct monitoring of injury rather than a secondary consequence of injury—a delayed reduction in GFR. By comparison to the field of cardiology we would move from a state of using changes in cardiac output or identification of heart failure as a reflection of myocardial injury to the use of troponin as a sensitive and specific marker of injury that physicians rely on and act upon. Of course there are other markers, besides troponin, that also provide additional information regarding the status of cardiac function. By analogy, multiple markers will be useful in nephrology, providing different information, for example about site of the injury, involvement of inflammation, and system associations. Some characteristics of an ideal biomarker are presented in Table 1. Biomarkers can be classified as predictive, prognostic, diagnostic, pharmacodynamic, or can be efficacy or surrogate markers (Table 2).

It is well recognized by regulatory agencies that a biomarker will not necessarily be informative in all contexts. In fact, the U.S. Food and Drug Administration (FDA) has developed a very thoughtful process by which they will “qualify” biomarkers in a “fit for purpose” contextualized way (2). There is a fundamental difference between “qualification” and “validation” of a biomarker. The latter term is best used to connote the validity and harmonization across many labs of the assay used to quantitate the biomarker.

In commenting on a major initiative of the FDA that focuses on biomarkers, Janet Woodcock, MD, current Director of the Center for Drug Evaluation and Research at the FDA, stated: “Most researchers agree that a new generation of predictive biomarkers would dramatically improve the efficiency of product development, help identify safety problems before a product is on the market (and even before it is tested in humans), and facilitate the development of new types of clinical trials that will produce better data faster” (3). The FDA has provided guidance that a biomarker can be considered “valid” if 1) it is measured in an analytical test system with well-established performance characteristics, and 2) there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test result (4).

There has been a great enthusiasm of the pharmaceutical industry to work with academia and the regulatory agencies to identify new biomarkers that will facilitate drug development. As a result, much progress has been made on the preclinical identification of biomarkers that identify kidney injury due to a wide variety of toxins as well as ischemia with a very high level of sensitivity and specificity. This predictive safety testing consortium (PSTC) explored in great detail a number of urinary biomarkers and presented the results to the FDA and the European Medicines Agency (EMA) simultaneously. This was the first use of a framework allowing submission of a single application to the two agencies. The FDA and EMA concluded that they will allow drug companies to submit the results of seven new tests that evaluate kidney toxicity—four for tubular injury (KIM-1, albumin, clusterin, and trefoil factor-3) and three for glomerular changes or impaired tubular absorption (cystatin C, total protein, and $\beta 2$ microglobulin) (5,6).

### Characteristics of an ideal blood or urinary biomarker

- Easy to measure with validated, reproducible technologies
- Stable in the blood or urine for time consistent with routine clinical use
- Devoid of interferences with other substances present in the biological fluid
- Unaffected by chemical composition of the fluid (e.g., urinary ionic strength and pH)
- Reflects risk, injury, outcome, and chronic sequelae with high sensitivity and high specificity
- Changes in measurements reflect efficacy of an intervention and/or recovery
- Identifies the specific site of injury (e.g., kidney tubule segment, glomerulus, endothelium, or interstitium)
- Understandable function of the marker in the kidney
Initially this resulted in a great deal of momentum, but things have stalled. Why is this the case? Why have we not moved more rapidly to translate these findings in rats to humans? In many cases, when examined closely, the mechanisms of injury observed in rats carry over to humans. When studying the sensitivity and specificity of biomarkers for kidney injury in the rodent the gold standard is histological injury. The PSTC consortium was meticulous in examining multiple regions of the nephron and multiple compartments (tubular, interstitial, tubule, cortex, and outer and inner medulla) of the kidney. In humans this is not possible. Even in those patients in which biopsy material is available, only a small portion of the kidney is sampled and is likely not to reflect overall injury in an acute setting. As a result, the biomarkers have been generally evaluated using sCr as a gold standard. This leads to faulty conclusions because sCr is so flawed as a gold standard for acute injury. There can be significant injury without a change in sCr, and sCr can change due to hemodynamic factors without injury. We have pointed out the large impact the faulty gold standard has on evaluation of biomarkers (7). This has resulted in a large number of clinical studies where the receiver operator curve analysis (a standard way to evaluate biomarkers) reveals an area under the curve that is often between 0.7 and 0.85, much lower than values of 0.9 to 0.99 that have been reported in animals (8,9). This has introduced a level of caution in researchers, practitioners, and the diagnosticians industry.

It can be argued that what really matters is not changes in laboratory values as an adjudicator of biomarker utility but longer term “hard” patient outcomes. While this is certainly true, it means that it may take many years to identify hard outcomes. For example, will an increase in a novel biomarker of kidney injury in a patient administered cisplatin, without a change in sCr, result in the development of hypertension and/or renal disease in later life? If we wait for these data we will lose the opportunity to employ these injury biomarkers. Especially in combination, they often provide a high negative predictive value even when compared to sCr.

Another reason for loss of momentum relates to studies of the kidney injury markers in chronic kidney disease (CKD). It is well known that acute kidney injury is associated with the development and/or progression of CKD (10). It therefore seems reasonable to assume these injury markers will predict progression of CKD, but the patient with CKD has multiple confounders that can potentially alter the rate of progression so that the relationship between a particular biomarker and progression is likely to be variable depending upon the study and the population—a fact that is being borne out in many studies. This does not, however, decrease the importance of a biomarker that provides mechanistic insight into an injury process that is important in the overall course of kidney disease. A list of some of the factors that have held back the study and the population—a fact that is being borne out in many studies.

In conclusion, over the last decade there has been intense interest in finding and qualifying new biomarkers of kidney injury. Biomarkers will enable us to diagnose kidney injury earlier and provide better information about the status of ongoing injury in patients with CKD as well as predict the likelihood of progression of disease. This will facilitate personalized medicine by better informing interventional, diagnostic, and therapeutic decision-making to minimize kidney injury and optimize interventional strategies. I am convinced that better kidney injury biomarkers will provide us with better tools that will result in better outcomes for our patients.

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Disclosures
Dr. Bonventre declares that he is co-inventor on KIM-1 patents that are assigned to Partners Healthcare. He is consultant to a number of companies in areas of patient kidney safety and development of new therapeutics including Sanofi, Thrasos, MediBeacon, Astellas, Matt, PTC, Keryx. He, or members of his family, own equity in Thrasos, Sensient, and MediBeacon.

References
Biomarkers in Chronic Kidney Disease

By Nisha Bansal and Chi-Yuan Hsu

There has been considerable interest in studying novel biomarkers in chronic kidney disease (CKD) beyond the conventional clinical indices, such as serum creatinine, blood urea nitrogen, and urine protein or urine albumin. The motivation for this is similar to what has been outlined in other articles in this issue of *ASN Kidney News*. For example, novel biomarkers may improve our ability to better risk classify patients and guide clinical actions (e.g., closer follow-up and more intense treatment for patients at higher risk of progression of CKD), to identify high-risk patients for enrollment into clinical trials (as enriched enrollment of patients who are more likely to progress will enhance study power), and to better understand underlying biological pathophysiological mechanisms (which may in turn identify novel targets for treatment).

Under the sponsorship of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a CKD Biomarker Consortium was formed in 2009. The consortium consists of investigators from more than a dozen academic medical centers and research institutions around the country, analyzing clinical data and stored biosamples and from numerous longitudinal cohorts.

**Biomarkers of renal injury in the setting of CKD**

One area of focus for the CKD Biomarker Consortium is to evaluate—among patients with CKD or those at high risk for CKD—urine injury biomarkers, many of which were initially identified in the arena of acute kidney injury (AKI). Examples of these urine injury biomarkers include urine kidney injury molecule-1 (KIM-1), urine neutrophil gelatinase associated lipocalin (NGAL), liver-type fatty acid binding protein (L-FABP) and beta-N-acetylgalactosaminidase (NAG).

Preliminary results show that injury biomarkers are in fact often detectable in the urines of patients with CKD, albeit usually at concentrations much lower than that seen in the setting of AKI. Interestingly, a minority of seemingly stable ambulatory CKD patients have very high levels (1,2). Several studies have shown that elevations of these levels of urine injury biomarkers are independent risk factors for more rapid loss of kidney function in subsequent years (1–3). For example, in the Chronic Renal Insufficiency Cohort (CRIC) study, although median urine NGAL concentration was only 17.2 ng/mL (in 3386 patients), 5 percent of readings were between 178.9 ng/mL and 3069.6 ng/mL (1). In that study, even after adjusting for potential confounders such as baseline estimated glomerular filtration rate (eGFR) or urine protein, high urine NGAL level remained an independent risk factor for progression of CKD, defined as halving of eGFR or end stage renal disease (Table 1). However, this novel marker only very modestly improved prediction of outcome events (1).

**Urine injury biomarkers may be associated with nonrenal outcomes**

Kidney dysfunction, as traditionally assessed by eGFR and urine albumin-creatinine ratio, is strongly linked with higher future risk of cardiovascular disease and death (4,5). Recent investigations have also noted that urine injury biomarkers may also be associated with cardiovascular disease and death. A study of approximately 3000 older adults in the Health, Aging and Body Composition cohort with and without CKD (mean eGFR 79 mL/min/1.73 m²) found that higher urine KIM-1 was independently associated with a 32 percent higher risk of incident heart failure, while there was no association of interleukin-18 (IL-18) with heart failure (6). In this same cohort, there was a modest association of higher urine KIM-1 with all-cause mortality (7). There was no association of KIM-1 with atherosclerotic disease and no association of IL-18 with atherosclerotic disease or death. However, the magnitude of the association of KIM-1 with higher risk of outcomes was smaller than that seen with urine albumin-creatinine ratio (6,7). These initial studies suggest that urine injury may possibly signal risk of numerous nonrenal outcomes. While these studies are observational and do not indicate causality, these data provide novel information about the link between kidney dysfunction and cardiovascular disease. Further studies are needed to explore these associations in different populations, including patients with known CKD.

**Urine injury biomarkers in unique patient populations**

Urine injury biomarkers have also been examined in unique populations, such as patients infected with the human immunodeficiency virus (HIV), AKI. In a study of 908 HIV-infected women with preserved kidney function (mean eGFR 88 mL/min/1.73 m²), high urine IL-18 levels were independently associated with 88 percent greater risk of all-cause mortality (8). There was no association of KIM-1 with higher risk of mortality (8). In this same cohort, IL-18 and KIM-1 were also independently associated with subsequent rapid decline of kidney function (9).

Interestingly, it has been suggested that elevations in urine injury biomarkers may also be an earlier manifestation of kidney injury induced by tenofovir, a commonly used nephrotoxic medication used to treat HIV. Among this cohort of HIV-infected women, three urine tubular biomarkers (NGAL, NAG and β-2-microglobulin) were measured before and after starting tenofovir (10). There were no differences in NGAL or NAG; however, β-2-microglobulin was 19 times more likely to be elevated after tenofovir initiation (10). In a cross-sectional study of 99 patients with HIV, of whom approximately half were on tenofovir therapy, spot concentrations of retinol-binding protein (RBP)—a low-molecular weight protein normally reabsorbed by the proximal tubule—were significantly higher in tenofovir users (11). As our understanding of these urine injury biomarkers increases, there may be further opportunities to study these biomarkers in other high-risk patient populations.

**Disclosures**

Dr. Hsu is a member of the CKD Biomarker Consortium. Abbott had donated urine biomarker assays (NGAL) to the CKD Biomarker Consortium. Dr. Bansal is supported by K23 DR08865; Dr. Hsu by U01 DK85649 and K24 DK92291.

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**References**

Biomarkers of Acute Kidney Injury

By Suneel M. Udani and Jay L. Koyner

Over the past decade there has been an explosion of research investigating biomarkers of acute kidney injury (AKI). The research was born out of the desire to replace serum creatinine, and in part urine output, as for a variety of reasons both serve as suboptimal tools in the diagnosis of acute renal tubular injury. The biomarker movement has been assisted by internationally accepted, standardized, consensus definitions of AKI. Whereas decades ago AKI definitions varied from study to study, the implementation and validation of the RIFLE (Risk, Injury, Failure, Loss and End Stage) and AKI Network criteria paved the way for the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (1). In solidifying the definition of AKI these criteria have helped to quantify the growing number of AKI cases, facilitated the growth of the AKI biomarker movement (2) from the 2004 Early ARF trial (investigating AKI in mixed medical-surgical intensive care units [ICUs]) or those from Parikh and colleagues from the TRIBE AKI (3,4) study (investigating AKI after adult and pediatric cardiac surgery) several biomarkers have been shown to detect AKI earlier than changes in serum creatinine. In these and other studies, many biomarkers (e.g., plasma and urine neutrophil gelatinase-associated lipocalin [NGAL], urine interleukin-18 [IL-18], or kidney injury molecule-1 [KIM-1]) demonstrated mild to moderate increase in serum creatinine.

Table 1. Biomarker performance in detecting AKI in a variety of clinical settings

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Perioperative AKI</th>
<th>Critically Ill</th>
<th>Emergency Room</th>
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<tbody>
<tr>
<td>Urine NGAL</td>
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<tr>
<td>Blood NGAL</td>
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<tr>
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<td>Urine KIM-1</td>
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<tr>
<td>Urine LFABP</td>
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<tr>
<td>TIMP-2/IGFBP-7</td>
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*AKI = acute kidney injury; CysC = cystatin C; IGFBP7 = insulin-like growth factor-binding protein 7; IL-18 = interleukin 18; KIM-1 = kidney injury molecule-1; LFABP = liver fatty acid binding protein; NGAL = neutrophil gelatinase associated lipocalin; op = operative; RRT = renal replacement therapy; TIMP-2 = tissue inhibitor of metalloproteinases-2; + = data published displays the ability to detect this aspect of AKI; – = data published does not display the ability to detect this aspect of AKI; ? = no large multicenter data published on this biomarker/aspect of AKI. Adapted and expanded from Koyner JL, Parikh CR. Clin J Am Soc Nephrol 2013; 8:1034–1042.
which only serve to confound the published literature. Finally, the ability to combine biomarkers to augment their diagnostic and prognostic performance remains statistically problematic.

In summary, there are several viable modern biomarkers of AKI. Each biomarker has its own individual profile, with some excelling at identifying early AKI while others can provide insight into the differential diagnosis of AKI (transient vs. intrinsic AKI). Over the last few years, undoubtedly new biomarkers will be discovered and established ones will be further validated. Eventually, biomarkers will be used as triggers for therapeutic AKI interventions or to risk-stratify patients to determine who would benefit from the early initiation of renal replacement therapy. Over the last decade nephrologists have laid the foundation for the next decade, which will see a shift towards these assays being used for clinical care while still being utilized in AKI research.

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Disclosure
Dr. Koyner reports receiving funds for enrolling patients in observational biomarker studies from Astute Medical and Abbott. He has received consulting fees from Astute Medical. Dr Koyner is funded by 1K23DK081616.

References
Kidney Disease Biomarkers

Biomarkers in Other Systemic Diseases: Cardio-Renal Syndrome

By W. H. Wilson Tang

Renal insufficiency is prevalent and clinically relevant in the setting of congestive heart failure. When admitted for acute decompensation, on average 1 out of 5 patients has a rise in serum creatinine, 1 out of 10 requires some form of dialysis, and 1 out of 20 requires long-term renal replacement therapies (1). These startling observations highlight the fact that adequate renal function plays a pivotal role in the clinical stability of heart failure. Hence, the term “cardio-renal syndrome” (CRS) has been coined to describe the extent of cardio-renal dysregulation whereby therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function (the 2004 National Heart, Lung, and Blood Institute [NHLBI] Working Group definition). However, the Acute Quality Dialysis Initiative (AQDI) has expanded this concept to a conceptual CRS classification scheme, which broadens the definitions to include a wide range of concomitant dysfunction between the heart and the kidneys (2). Unfortunately, such contemporary nomenclature is largely descriptive, and the lack of pathophysiologic basis has limited its clinical applicability in triaging distinct therapeutic approaches to individual patients while ignoring many confounding factors. Indeed, when both heart and kidney impairment progresses, as indicated by rising natriuretic peptide levels and worsening glomerular filtration rate, the long-term outcomes are the poorest (3). Nevertheless, the prognostic value of natriuretic peptides remains robust even though the range of the absolute values are higher than those without renal insufficiency.

There is a natural tendency for clinicians, researchers, and investigators alike to gravitate on quantifying renal dysfunction with an easily available metric that is useful in outcomes research. Indeed, a concerted effort was made to examine the clinical relevance of changes in daily serum creatinine during heart failure hospitalization. A rise in serum creatinine ≥0.3 mg/dL was deemed to provide the optimal sensitivity (65 percent) and specificity (81 percent) in predicting in-hospital mortality (4)—a threshold that has been used (and perhaps misused in retrospect) over the past decade in a wide range of outcomes research studies. Such a creatinine rise in patients (often termed “worsening renal function” or WRF) has been associated with an increase in length of hospital stay by 2.5 days, a 67 percent increase in risk of death within 6 months after discharge, and a 33 percent increased risk for readmission (5). However, several new observations have recently emerged regarding the complexity of creatinine changes during decongestive therapy and what they may imply. Improvement in renal function following decongestive therapy may not always reflect better clinical status, as evident that those whose fall in serum creatinine requires progressive renal impairment prior to admission (6). At the other end of the spectrum, the ability to achieve sustained decongestion despite worsening renal function (as evident by evolving hemoconcentration) has been associated with paradoxically better outcomes (7). Interestingly, the main determinants of worsening renal function during decongestion appeared to be inadequate systemic perfusion pressure (i.e., drop in systemic blood pressure during treatment) as well as inadequate responses to decongestive therapy (i.e., drop in net urine output) rather than changes in central hemodynamics or acute tubular injury as determined by novel AKI biomarkers (8–10, Figure 1). These contemporary observations have thus revealed the increasingly clear picture that creatinine-based concepts of CRS may not account for concomitant large intravascular fluid shifts and the lack of true nephrotoxicity during aggressive decongestion—a concept that is still in evolution. Nevertheless, the good news is that not all rises in creatinine during decongestion for decompensated heart failure signal the grave consequence of AKI.

Perhaps the biggest challenge in contemporary approaches to CRS is the lack of effective “renal-sparing” or “renal-enhancing” therapies in the treatment of congestion for patients with heart failure. Much effort has been made over the past decade by investigators and industries alike. These included the clinical development of natriuretic peptide analogues, adenosine receptor antagonists, vasopressin receptor antagonists, and ultrafiltration—all have met with mixed results or off-target effects. Indeed, the treatment approach to acute decompensated heart failure has not changed over the past 5 decades, with the sole reliance on intravenous loop diuretics in various forms of dosing, route, and formulations, plus some adjunctive therapeutics. While future insightful mechanism biomarkers to guide therapeutic choices are still needed, they are more likely to be utilized to prevent rather than to react to AKI.

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References
Biomarkers in Acute Kidney Injury in Cirrhosis

By Daniel E. Carl and Arun J. Sanyal

Cirrhosis is a major contributor to the burden of disease in society, and much of the morbidity and mortality associated with cirrhosis is due to the complications of portal hypertension. Acute kidney injury (AKI) is a frequent complication in patients with cirrhosis, occurring in up to 20 percent of hospitalized patients (1). Despite the high rate of AKI in this patient population, there is often a delay in early diagnosis of AKI. Furthermore, there are clinical challenges in correctly diagnosing the etiology of AKI, which in turn can alter specific therapy. This article will focus on the current pitfalls in diagnosing AKI in cirrhosis and the use of biomarkers in this population.

The etiology of AKI in cirrhosis is often separated by functional and structural forms of injury. Approximately one-third of AKI occurrences in hospitalized patients with cirrhosis is from acute tubular necrosis (ATN), although the less common glomerular injury also needs to be screened. The remaining forms of AKI occur from decreased renal perfusion. The majority of these are volume-responsive prerenal azotemia (PRAD), which accounts for approximately 45 percent of the AKI in the cirrhotic population. However, the other third of patients with AKI from decreased renal perfusion are not volume responsive, and have hepatorenal syndrome (HRS) (1). As treatment is different for each of these three types of AKI, the correct diagnosis is imperative. For example, HRS is treated with the vasoconstrictor agents norepinephrine, terlipressin, or midodrine in addition to albumin rescue (2,3). In addition, early diagnosis and subsequent treatment of HRS portends a better renal prognosis (4). The etiology of AKI can also dictate whether renal replacement is offered; specifically, patients not deemed a liver transplant candidate who are diagnosed with HRS are often not offered therapy. However, the converse is true in patients diagnosed with ATN, and missing the diagnosis of ATN can lead to denial of renal support to a patient. Further muddying the picture, infections are common in cirrhotic patients and can independently lead to all three types of AKI (ATN, PRA, and HRS); AKI in these patients may represent a continuum from functional to structural AKI.

The clinician is investigating the etiology of AKI in cirrhosis, common studies used include: serum creatinine, urinalysis evaluation, urine sodium and fractional excretion of sodium (FENA), and urine microscopy evaluation. A percutaneous kidney biopsy could help in the correct diagnosis; however, it is frequently not performed in this patient population because of bleeding concerns. Wade et al. (5) performed kidney biopsies in cirrhotic patients undergoing a liver transplant and found 41 percent had ATN despite non-classic urinary findings, which highlights the common yet likely undiagnosed ATN lesion in cirrhosis. As prompt recognition and diagnosis of HRS is crucial in the management of the disease, it is important to know the limitations of current methods to estimate GFR and indices of evaluating AKI. Traditional methods of estimating GFR may be less reliable in cirrhosis compared to the general population, as both urea and creatinine production can be altered in cirrhosis. In addition, cirrhotic patients may have deceivingly low creatinine values, despite the presence of muscle mass loss, as this can occur more decreased muscle mass (6), increased renal tubular secretion of creatinine (7), as well as decreased hepatic creatine synthesis. Accordingly, it is well documented that cirrhotic patients can have a normal serum creatinine despite having a truly depressed GFR (6,8). Indeed, both measured as well as calculated creatinine clearances are falsely elevated in cirrhotic patients, and can overestimate inulin clearances by up to 74 percent (9). Traditionally, clinicians have used urine sodium, osmolality, as well as evaluation of urine sediment to help differentiate HRS from other causes of AKI. However, caution should be exercised with these traditional markers of renal function to evaluate the possibility of HRS. For example, patients with ATN in the setting of cirrhosis can have a low urinary sodium concentration, potentially a result from prolonged renal vasconstriction (10). Conversely, patients with HRS and hyperbilirubinemia can infrequently have high urine sodium values (11,12). Furthermore, granular casts typically associated with ATN can also occur with persistent hyperbilirubinemia in HRS. As a result of these inconsistencies with urinary markers to differentiate ATN from HRS, the International Ascites Club removed these indices with publication of their revised guidelines in 2007 (13).

In summary, it is paramount to both diagnose AKI early as well as differentiate structural from a functional type of AKI. Serum creatinine is subject to many pitfalls in cirrhosis, and is also a late marker of kidney injury. Furthermore, it does not segregate between structural and functional AKI, particularly in cirrhosis. To this end, there has been a growing interest in nephrology to find and validate markers of structural kidney injury, especially those that will precede serum creatinine elevations. Interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein (L-FABP), and neutrophil gelatinase associated lipocalin (NGAL) appear to have the most promise in defining structural, rather than functional, injury in this patient set.

Two studies separately investigated the utility of uNGAL in differentiating structural (ATN) from functional (PRA or HRS). In the first, Fagundes et al. (14) studied urinary uNGAL levels in 241 patients with cirrhosis, 84 of whom had renal dysfunction. They found uNGAL levels were significantly higher in those with ATN compared to PRA or HRS. uNGAL levels in HRS patients were at a level between ATN and PRA. Moreover, upon review of the HRS cohort, uNGAL levels were higher in patients with an infected medici event compared to those who did not have an infection. Moreover, in this subset, uNGAL levels were close to those with ATN. In a second study, Verna et al. (15) measured uNGAL levels in 118 cirrhotic patients admitted to a single hospital. Similar to the preceding study, they also found uNGAL levels significantly higher in patients with intrinsic AKI compared to HRS or PRA, with uNGAL levels in HRS patients intermediated between the two groups. This difference in uNGAL between HRS and intrinsic AKI was in the absence of any difference in serum creatinine. Collectively, these two studies highlighted the promise uNGAL has in differentiating the different forms of AKI.

Finally, Belcher et al. (16) evaluated 76 patients with progressive AKI in a prospective, multicenter, blinder study. They found 53 percent had ATN, with the remainder having PRA (26 percent) or HRS (22 percent). FENA was lowest in the cohort diagnosed with HRS, although not statistically different from PRA or ATN. NGAL, L-FABP, IL-18, and KIM-1 were measured in all patients. The etiology of AKI was determined in a blinded manner, without knowledge of the biomarkers. Those identified with ATN had the highest levels of all four biomarkers in the intermediate range similar to the two prior studies. Moreover, Belcher et al. found absolute value cutoffs for all four biomarkers to define those with ATN. The relative risk of ATN increased with the increasing number of positive biomarkers. In those patients with none of the four biomarkers above the cutoff, 17 percent had ATN. This increased to 73 percent if two of the biomarkers were positive and to 100 percent if all four were positive.

In conclusion, AKI in the cirrhotic population is a frequently encountered clinical problem, and is associated with a high mortality. Because of limitations in available laboratory tests, the diagnosis of AKI is frequently delayed and the etiology of AKI is incorrect. The introduction of new biomarkers that increase earlier than traditional markers, such as serum creatinine, allows for earlier identification of renal injury. Furthermore, these biomarkers hold promise for delineating structural versus functional AKI.

References

Biomarkers in Contrast-Induced Acute Kidney Injury

By Steven D. Weisbord, MD, MSc

Contrast-induced acute kidney injury (CI-AKI) is a common condition that is associated with serious, adverse short- and long-term outcomes. Despite substantial advancements in our understanding of CI-AKI, the capacity to effectively risk-stratify patients, diagnose incipient renal injury before elevations in serum creatinine (SCr) manifest, and identify patients at highest risk for adverse downstream events is limited. Blood and urine biomarkers of kidney injury hold promise as a means by which the risk-stratification, diagnosis, and prediction of prognosis of CI-AKI could be significantly enhanced, and the judicious implementation of cost-effective preventive care and treatment to mitigate adverse outcomes substantially improved.

Renal tubular injury in CI-AKI, which results from medullary hypoxia, generation of reactive oxygen species, and direct tubular toxicity of contrast media, occurs almost immediately following contrast administration. In a rat model of CI-AKI, Liss et al. (1) demonstrated a reduction in outer medullary renal blood flow within minutes of contrast administration, with the most pronounced decrement occurring within 10 to 20 minutes. Bakris et al. (2) documented increased oxygen free radical generation within 5 minutes and reduction in glomerular filtration of nearly 50 percent less than 20 minutes following contrast administration in dogs. Hofmann et al. (3) demonstrated that medullary blood flow in healthy human subjects decreased within 20 minutes following intravascular contrast administration. These and other studies confirm that the adverse hemodynamic and nephrotoxic effects of iodinated contrast develop within minutes following contrast administration. However, the diagnosis of CI-AKI in clinical practice is based on identifying elevations in SCr that typically manifest days following contrast administration. Consequently, provider and patient awareness of the development of CI-AKI is delayed or may not occur at all if follow-up assessment of SCr is not performed. As a result, supportive care to mitigate kidney damage, including correction of intravascular volume depletion and withdrawal of potentially nephrotoxic medications, may be delayed or not implemented. This lag in diagnosis underscores the strong need to identify other blood and/or urine markers that are sensitive and specific for early renal tubular injury, that identify patients with CI-AKI at the time of initial kidney insult, and that help inform the provision of appropriate care to attenuate the risk for progressive kidney damage.

Figure 1. Pathophysiology of contrast-induced acute kidney injury and timing of events

Nakamura et al. (11) demonstrated that postangiography urinary liver fatty acid binding protein (L-FABP) levels were higher among patients who developed CI-AKI than patients who did not (18.5±12.8 μg/g vs. 7.4±4.4 μg/g; p<0.01). Postangiography L-FABP levels increased among patients with CI-AKI, yet remained unchanged in patients without CI-AKI (46.8±30.5 μg/g vs. 8.0±6.2 μg/g; p<0.001). A subsequent study by Hirsch (8) demonstrated higher concentrations of urine neutrophil gelatinase-associated lipocalin (NGAL) (155±32 ng/mL vs. 11.6±2 ng/mL; p<0.001) and plasma NGAL (151±34 ng/mL vs. 36±4 ng/mL; p<0.001) 2 hours following angiography in patients with CI-AKI compared to patients without CI-AKI. Urine and plasma NGAL at 2 hours were strong independent predictors of CI-AKI (p<0.0001, respectively). In a study of 150 patients, Ling et al. (9) demonstrated that in addition to diagnosing kidney injury earlier than SCr, urine interleukin-18 (IL-18) levels 24 hours postangiography predicted the development of major adverse cardiac events over 17 months of follow-up (relative risk [RR] =2.09; p=0.001). More recently, in a study of 410 patients with CKD undergoing angiography, Briguori et al. (13) demonstrated that elevations in serum cystatin C (CyC) of ≥10 percent at 24 hours were 100 percent sensitive and 86 percent specific for the development of CI-AKI and were predictive of 1-year death and need for dialysis. Moreover, this threshold increase in serum CyC was more predictive of 1-year death and need for dialysis than elevations in SCr.

Notwithstanding these promising preliminary findings, there are certain methodological limitations to these studies. First, a large proportion of patients did not have baseline CKD, which is the principal risk factor for CI-AKI; consequently only a small minority developed CI-AKI. Second, since biomarker levels may be affected by baseline kidney function, the generalizability of findings from many of these studies to subjects with baseline CKD is not clear. Third, most studies did not track longer term outcomes. Thus, little is known about the ability of biomarkers to predict progressive kidney disease and other adverse events following CI-AKI. Lastly, several studies examined just one bio-

Prior studies of biomarkers in CI-AKI

Over the past decade there have been many studies investigating biomarkers for the risk stratification, diagnosis, and long-term prognosis of AKI. These studies focused largely on renal injury in the postoperative and intensive care unit settings. The predictive, diagnostic, and prognostic capacity of biomarkers in the context of iodinated contrast administration has been less well characterized. However, the studies that have been conducted to date demonstrate the potentially important role biomarkers may play in the setting of CI-AKI (Table 1) (4–15).

Table 1. Studies of biomarkers and contrast-induced acute kidney injury

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts (N)</th>
<th>Pts with CKD (N)</th>
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<td>Briguori et al</td>
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Figure 1. Pathophysiology of contrast-induced acute kidney injury and timing of events
marker rather than a panel of biomarkers, limiting the capacity to determine if combinations of biomarkers are more predictive than a single biomarker. Notwithstanding these limitations, the findings of these studies suggest that biomarkers could potentially improve the ability to risk stratify patients, diagnose early CI-AKI, and identify risk for serious, adverse longer term sequelae.

CI-AKI is a common condition associated with adverse outcomes. Notwithstanding advancements in our understanding of risk factors for, pathophysiology of, and potential adverse events associated with CI-AKI, there remain significant limitations in our capacity to effectively and efficiently prevent, treat, and limit longer term effects of CI-AKI. Preliminary studies of blood and urine biomarkers in the setting of contrast administration suggest that biomarkers may be a means by which the care for patients at risk for and with CI-AKI could be improved. Large, well-designed studies that measure panels of biomarkers and that provide the opportunity to investigate “yet to be identified” biomarkers are needed to inform the delivery of evidence-based, effective care for the prevention and treatment of this iatrogenic condition.

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Disclosure
The opinions expressed in this article are those of the author and do not reflect the views of the Department of Veterans Affairs or the U.S. government.

References
Emerging lessons in how to use “big data” about how “big data” should be used to create accurate predictions (2). As dramatized in the movie “Moneyball,” the use of rich baseball databases added a statistical dimension to decision making in that sport, which had previously been based on expert opinion. The key was that the database included hard outcomes on which to train predictive equations—“Ws and Ls,” wins and losses. Predictions from big databases in cancer are emerging using the same principle, capturing hard outcomes to build predictive equations using high dimensionality molecular platforms. Such predictions of the true disease state should be: 1) Bayesian, acknowledging prior probabilities and biases; 2) probabilistic, with estimates of potential for error; 3) updatable with new knowledge; and 4) consensus-seeking, including expert opinion.

The challenge is to assemble these pieces of information into an understanding for the individual patient (Figure 2).

Developing the Molecular Microscope

Using these principles, we developed a system for kidney transplant biopsy assessment, as recently reviewed (3). Our stepwise analysis is outlined in Table 1.

Our project related molecular changes in kidney biopsies to histologic changes, clinical phenotype (function, proteinuria, etc.), and outcomes, as well as specific diseases. We used indication biopsies as the centerpiece for disease understanding and reclassification. The project has captured more than 1000 indication biopsies from kidney transplant recipients and defined relationships among function, histologic, outcome, and molecular changes measured by microarrays. Our understanding was helped by characterizing gene sets associated withologic changes in mouse models, permitting a sketch of the underlying biology—infarction and activation of macrophages and effector T cells, tubulo-interstitial injury, and microcirculation injury, the types of diffuse changes that can be detected in a core biopsy.

We found that the prevailing classifications of diseases in transplants had major errors, for example interpretation of staining for complement factor C4d (4). We reclassified the diseases states based on conventional and molecular assessments. These biopsies became our reference set against which new biopsies can be assessed. We developed equations to turn microarray results into estimates of the diseases and the degree of tissue injury, and validated and calibrated the readouts. We integrate this with conventional assessments to create an overall view, which we envisage as that assembled by the clinician, not the pathologist.

The result is the Molecular Microscope system of equations, which currently provides estimates of the probability of: 1) T cell-mediated rejection (TCMR) score; 2) antibody-mediated rejection (ABMR) score; 3) atrophy-scarring score—extent of chronic damage; 4) acute kidney injury score—extent of recent parenchymal injury and ongoing injury repair; and 5) prognosis—the risk of progression to failure.

Lessons

The molecular phenotype of a biopsy is a reproducible dimension of the biopsy, but time and experience will be needed to define its full meaning. The molecular changes correlate with histologic and clinical phenotypes, but do not necessarily “agree” with them and are generally superior to histologic or clinical parameters in predicting prognosis. The combined values of the molecular, histologic, and clinical assessments represent an opportunity for a consensus, not competition. Our goal for each biopsy and for each patient is to assign numerical values in multidimensional space, where N=1, a step toward precision medicine, and can be compared to her nearest neighbors in the reference set.

For example, the TCMR score is virtually always abnormal in typical TCMR, but there is considerable disagreement, which includes false negative histologic assessment of scarred tissue, confusing situations such as polyomavirus with TCMR, and false positive histologic diagnoses caused by sharing of lesions with other diseases. The ABMR score, on the other hand, must assess a much more complex and pleiotropic phenotype. ABMR has a large dynamic range, from fulminant to indolent to inactive, and accrues time-dependent changes in the microcirculation. The ABMR molecular score may not be positive in patients who have relatively inactive ABMR. This is a new phenotype—histologic ABMR with low molecular activity. The histologic, clinical, and molecular states together create new disease classes, as has already happened in cancer, where complex multidimensional phenotypes are emerging as molecular measurements become standard of care.

The implication for biomarkers in body fluids is not necessarily bleak. They cannot provide the richness of phenotypic detail needed for disease reclassification and creation of new phenotypes, and as measurements in one dimension are unlikely to answer the unmet need for precision medicine. However, biomarkers in body fluids can be re-examined as useful additions to new multidimensional disease classifications to see how they contribute to care in the clinic, for example monitoring after biopsy.

By Philip F. Halloran

Biomarkers in Kidney Transplantation: The Key is Disease Reclassification, Starting at The Biopsy

Kidney Disease Biomarkers

Philip F. Halloran, MD, PhD, is affiliated with the University of Alberta and the Alberta Transplant Genomics Centre in Edmonton, AB, Canada.

References

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Table 1. Steps in molecular biopsy phenotyping

- Focus on indication biopsies: phenotype
- Granularity: clinical, lab, histology, molecular
- Annotate the molecules: pathogenesis-based transcript sets – http://atagc.med.ualberta.ca/
- Discover the molecular classes – cross-validate
- Validate in new biopsy set
- Engineer the reporting system
- Calibrate the readouts: real time clinical meaning
By Christine King

The burden of renal disease is continuing to increase not only in the U.S., population but worldwide, as comorbidity factors such as obesity and diabetes become more prevalent (1). This year, the CDC estimates that more than 10 percent of adults in the United States, approximately 20 million people, may have chronic kidney disease (CKD) in varying degrees of severity, with many people being unaware that they either have CKD or are at increased risk of developing it (2).

The prevalence of CKD, now and in the future, truly represents a public health challenge. The area of renal biomarker research holds much promise, as it offers the potential to address the challenge of predicting and identifying renal injury, staging it, and monitoring the effectiveness of therapies. However, innovators often feel stymied by the regulatory requirements in obtaining clearance or approval for new devices. So, perhaps a more appropriate question for renal biomarker researchers and manufacturers is not “Biomarkers and the FDA—are we there yet?”, but rather “Biomarkers and the FDA—where do we start?”

The regulatory process and criteria used by the Center for Devices and Radiological Health/Office of In Vitro Diagnostics and Radiological Health (CDRH/OIR) for evaluating the safety and effectiveness of biomarker devices are the same as with any diagnostic device. The FDA classifies all devices by risk. In other words, what is the impact of an incorrect result on the intended use population?

The amount of risk associated with a new device is dependent on its intended use. The intended use should state the purpose of the device, such as diagnosis, prognosis, monitoring, stratifying, or identifying specific populations. It should also specify the targeted population for the biomarker test such as renal allograft recipients, diabetics, or patients undergoing chemotherapy. The intended use and its designated population can be specific or broad depending on the purpose of the biomarker assay. The intended use should be formulated after the basic research and feasibility of the new biomarker and its assay has been completed and evaluated. These initial studies should be robust for characterizing the biomarker “fit for purpose” by defining the clinical conditions under which the biomarker is to be used, and for the analytical validation of the assay used to measure the biomarker.

Feasibility studies should be designed to test the clinical hypothesis for the validity of the biomarker test in a small sampling of the proposed intended use population. It is during this phase of development that any applicable clinical cutoffs or algorithms are tested and then “locked” prior to commencing the pivotal clinical trial. The pivotal trial should validate the performance of the locked cutoffs and/or algorithms in the intended use population. If the data from the pivotal trial indicate that the cutoffs or algorithm(s) need to be modified to meet the intended use of the device, then a new pivotal study will need to be performed to validate the new cutoff algorithm.

Analytical validity means that the device performance is reproducible over time (precision), specific for the target biomarker, and accurate. Analytical validity also could encompass linearity; detection limits (e.g., limit of the blank, limit of detection, and limit of quantitation); stability of the sample, reagent, controls and calibrators; and definition of a measuring range. The final submission to the FDA should include validation of analytical validity in addition to the clinical validity of the biomarker assay.

The pivotal clinical study to support the indications for use should be well designed to ensure that the right data, rather than just more data, is collected. The study populations should be appropriate for the intended use of the biomarker test, whether the use is diagnostic or prognostic, and should include individuals who represent the intended test population, including those who have or are at risk for developing the disease or condition. Sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) should be evaluated to determine how well the biomarker test is able to distinguish between those who have or are at risk for developing the disease or condition and those who are not.

Study end points also need to be considered in pivotal studies. The selection criteria should include how measurable or definable the end point is, and whether the intended use of the biomarker device should be supported by a single, or multiple end points. Regardless of the number of end points, the acceptable performance criterion for the biomarker device and its ability to meet the end point(s) should be established prior to beginning the pivotal study. Also, if multiple end points are used, each end point should be distinguishable from the others in the study in order to prevent “double counting” of results and reduce variability or bias in outcome reporting.

Correlation with clinical diagnosis is one example of an end point. This end point is often used for diagnostic biomarker tests where the results of the device are compared to diagnosis of a disease or condition in the study population per current clinical practice or guidelines. Ideally, this type of study should include several different test sites—large and small, urban and rural—to account for variability in clinical practice, comorbidities, and patient demographics.

Longitudinal end points or outcomes may be appropriate for pivotal studies, especially for prognostic biomarkers. However, duration of the study and participant dropout are factors to be considered in this type of study design.

Studies may be performed prospectively or retrospectively. There are advantages and disadvantages to each type of design. The advantage to a prospective study is that the study conditions can be well defined for the particular intended use of the biomarker device. A disadvantage is that it may be difficult to determine the disease/condition prevalence in prospective studies so that there is inadequate statistical power. It may also be difficult to estimate the length of time needed for the subject to reach the end point.

Retrospective data or samples may be used; however, the study protocol under which the samples were collected and stored needs to be well documented. The patient population, disease prevalence, and study population in a retrospective study needs to be the same as that specified in the intended use of the new biomarker device to avoid bias in the data, such as selection bias. Biomarker stability in the stored samples must be validated prior to beginning the pivotal study to determine whether retrospective testing will adequately substitute for prospective testing.

Some pitfalls to avoid when using retrospective study samples include the following: 1) the retrospective inclusion/exclusion criteria may not be appropriate for the intended use of the new biomarker; 2) samples or data may be missing; 3) the patient demographics may not mimic or match the intended use population; and 4) the biomarker recovery between the retrospective study and the intended use population may not be the same, or the prevalence of the disease or condition as defined by the intended use may not be the same. The impact of the differences may prevent accurate calculations of PPV and NPV, or determination of risk. Additional information on FDA’s current thinking on clinical study design for in vitro diagnostic devices can be found in FDA guidance documentation (3).

This has been only a brief discussion of “Where do we start?!” for biomarker tests and the FDA. There is a mechanism for early interaction between the FDA and sponsors called the “Pre-Submission process. Sponsors may submit their proposed study design to FDA for feedback (4). The process is informal and flexible and the FDA encourages this interaction early in the biomarker test development so that safe and effective new biomarkers for renal disease may soon be available to the public.

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References
Clinicians view kidney disease as a continuum where kidney failure results from a combination of patient susceptibility factors (diabetes, hypertension, or low nephron mass) combined with episodes of kidney injury (acute kidney injury [AKI]). Clinicians use traditional biomarkers such as serum creatinine, urine output, and albumin as indices of kidney function to diagnose, prognosticate, implement therapy, and monitor progression. These traditional biomarkers are far from ideal. Serum creatinine is a surrogate for kidney function, not injury, and often only signals the injury after several days. Creatinine is also a poor surrogate for renal reserve in assessing patients for chronic kidney disease (CKD) as more than 50 percent of a patient’s nephrons have to be nonfunctional before it will increase. Urine output is hindered by diuretic use, inaccurate collection, and the lack of intactness (1). There are many etiologies that lead to renal disease and complex compartments within the kidney that can be injured (vasculature, interstitium, glomeruli, and tubules). These factors make the development of specific biomarkers and the interpretation of these markers particularly challenging, but nonetheless critically important to assist the clinical nephrologist.

Biomarkers in AKI

Clinicians are challenged to recognize early and identify quickly the underlying causes of AKI in order to implement the appropriate therapies that may reduce the risk of progressive kidney disease. For example, many biomarkers have been tested to determine if they can differentiate patients from intrinsic AKI with the latter due to tubule injury from medications, sepsis, or ischemic injury (2). During clinical AKI, there are alterations in the renal microcirculation and tissue oxygenation that ultimately lead to early cellular injury when cells release these markers into the plasma or urine where they provide a window into the local environment (1). Therefore, the baseline health of the kidney and the cumulative damage leading up to the episode of AKI play a role in the response to injury (1) and affect how we interpret these biomarkers.

Promising diagnostic markers of renal function and damage include cystatin C, neuropilin gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), insulin-like growth factor (IL-18), and liver fatty acid binding protein (L-FABP). Each of these markers provides information regarding a different part of the nephron (3). Cystatin C is a small protein produced by all cells that is freely filtered and degraded by the proximal tubule and has become a clinically utilized biomarker. Also with glomerular injury and a disruption of the filtration barrier, albumin is excreted in the urine. When there is a tubular injury both albumin and cystatin C are not reabsorbed and are excreted in the urine. There are also markers that are released from damaged cells (N-Acetylβ-β-glucosaminidase [NAG], α-glutathione-S-transferase [GST], γ-GST, and others) that increase in response to inflammation and oxidative stress (NGAL, KIM-1, L-FABP, and IL-18), NGAL is an iron-carrying protein that has been extensively studied with many attractive traits as a biomarker for AKI. It increases quickly within hours of renal injury and is both sensitive and specific. KIM-1 is also a promising marker for the detection of AKI as it is produced during proximal tubule injury and may be particularly useful in determining drug toxicity. These biomarkers open the door to patients with "subclinical AKI" who have undetectable changes in creatinine, but an increase in biomarkers reflecting kidney damage (3,7). In the current state of development, novel biomarkers must be interpreted with caution as not all perform well in every AKI setting (2).

Just as there are various segments of each nephron subject to injury, there are various causes of renal injury. Some injuries—such as cardiac surgery, contrast nephropathy, and nephrotoxins—have a known time of exposure, making clinical studies more straightforward. In other clinical scenarios, such as sepsis and hepatorenal disease, the time course and the primary injury can be obscured.

Beyond predicting the development of AKI, some biomarkers have been able to prognosticate severity and duration of AKI, likelihood for renal replacement therapy (RRT), and recovery of function and death (4). These predictions appear to be stronger in the population where the timing of the renal insult is known (cardiac surgery) (4). An ongoing dilemma in renal biomarker research is what should be the gold standard for the validation of these novel biomarkers. Just demonstrating the superiority to serum creatinine or urine output is a flawed approach and correlation between biomarkers and histologic damage does not occur in clinical trials. Therefore, the outcomes in AKI will not likely change until we gauge a biomarker’s worth by its ability to provide a trigger for a clinical action (initiate or monitor therapy) (4). The association between these biomarkers and clinically relevant outcomes is needed (3).

There are still significant challenges in AKI biomarker research. First, we need to address patients with underlying CKD or in a setting where the renal health of the patient is not known prior to AKI (2). Second, we have to assess the usefulness of a biomarker to predict the progression to CKD as the time course may be long and variable. Finally, cutoffs for various markers, bedside utility, platform standardization, interlaboratory calibration (4), and the cost-benefit ratio of these biomarkers are all areas to address.

Biomarkers in CKD

Nephrologists require improved tools for the early diagnosis of the 26 million adult Americans who suffer from CKD and are at risk for developing ESRD (5). The most commonly utilized and validated biomarkers in CKD are eGFR and proteinuria. Similarly to AKI biomarkers, these biomarkers are retrospective or insensitive. Novel biomarkers are being studied in tubulointerstitial injury, glomerular injury, endolymphatic dysfunction, oxidative stress, inflammation, and fibrosis. As it is becoming more recognized that AKI is a prelude to CKD, the biomarkers assessed in AKI are also being tested in the setting of CKD (5).

Cystatin C, β-trace protein (BTP), and uric acid have been used as surrogates for kidney function, but require novel markers with validation in larger populations and are not being used in clinical practice (5). In clinical studies, NGAL concentration correlated to CKD staging, validated in various etiologies of CKD, and predicted kidney function decline. Other tubulointerstitial markers—such as KIM-1, NAG, and L-FABP—still need long-term studies in larger populations to ensure their validity as markers in CKD (5). Newer biomarkers sensitive to glomerular injury, such as nephrin, podocin, and podocalyxin, have been assessed in lupus, postinfectious, and IgA nephritis, and in their early stages seem to be specific to glomerular diseases (5).

Other markers, such as C-reactive protein and IL-18, markers of inflammation and fibrosis, are being assessed in progressive kidney disease (5). Specific pathophysiologic mechanisms of primary renal diseases leading to CKD and elements of CKD progression are shared by all forms of progressive CKD, such as the progression of diabetic nephropathy, and nephrotoxins—have a known time of exposure, making clinical studies more straightforward. In other clinical scenarios, such as sepsis and hepatorenal disease, the time course and the primary injury can be obscured.

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Biomarkers in transplantation

There is a large effort to investigate novel biomarkers that could guide titration of immunosuppressive medications tailored to the biologic suitability of the graft and recipient (6). Studies have unmasked a genetic signature that was highly sensitive and specific in patients experiencing chronic renal allograft rejection or tolerance (6). Additionally, urine proteomic analysis can distinguish chronic allograft injury from healthy controls and those patients with excellent graft function (6). Although promising, this area of research needs significantly more validation in a prospective fashion with larger cohorts of patients with attention to graft protection (6).

In summary, there is an intensive effort to develop novel biomarkers of kidney disease as currently used clinical biomarkers have shortcomings. There is hope, however, for implementing point-of-care use of panels of biomarkers in the near future. For the clinician, such tools will assist in therapy and counseling of their patients with the goal of improving outcomes.

Jennifer R. Charlton, MD, is an Assistant Professor of Pediatrics, Division of Pediatric Nephrology, and Mark D. Okusa, MD, FASN, is the John C. Buchanan Distinguished Professor of Medicine at the University of Virginia Health System in Charlottesville, VA.

References

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Policy Update

Kidney Community Unites to Raise Awareness on Capitol Hill

By Kevin F. Erickson, MD, and Mallika L. Mendu, MD, MBA

On May 1, 2014, kidney patient and health professional advocates gathered in Washington, DC, for Kidney Community Advocacy Day. Since 2010, ASN has organized an annual congressional advocacy day to raise awareness about kidney disease and promote issues important to the kidney community. Building on the momentum from the first-ever Summit of U.S. Kidney Organizations at the society’s annual scientific meeting in 2013, more than 100 advocates from 14 organizations met with 133 congressional offices, including 19 members of Congress—triple the number of participants and double the number of meetings from ASN’s congressional advocacy day in 2013.

All the advocates were divided into state teams and met with members of their congressional delegation to promote increased funding for kidney research and the Comprehensive Immunosuppressive Drug Coverage Act of 2013.

Kidney research funding

More than 20 million Americans have kidney disease, which can have a significant effect on patients’ health and quality of life. When patients’ kidneys stop working, they need a kidney transplant or dialysis. Dialysis continues to be associated with high morbidity, mortality, and costs. Since the federal government pays for most of dialysis care, it has a significant incentive to fund research to prevent kidney disease progression and improve the health of patients on dialysis.

Yet kidney disease remains underfunded relative to other diseases; total federal investments in kidney research equal less than 1 percent of the federal cost for providing kidney disease care. Kidney Community Advocacy Day participants asked for an additional $150 million per year for 10 years above current funding levels to help address this disparity. More research will lead to better ways to diagnose, prevent, and treat kidney diseases of all kinds, improving the health of millions of Americans as well as reducing total federal expenses.

Comprehensive Immunosuppressive Drug Coverage Act of 2013

All patients with kidney failure receive Medicare coverage. For most patients with kidney failure, transplants are the optimal therapy. Medicare pays for kidney transplants, but only provides 36 months of immunosuppressive drug coverage for patients who do not qualify for Medicare because of age.

After 36 months, patients must find a way to pay for the expensive immunosuppressive drugs, and many patients have difficulty affording these medications. Because immunosuppressive medications are necessary to preserve the function of transplanted kidneys, some patients lose their transplanted kidney when they encounter difficulties in affording these medications and are forced to reduce or discontinue the prescribed treatment driven by economic necessity.

This is a tragedy for patients, their loved ones, and kidney donors who have provided a precious gift. In addition, patients return to dialysis when their transplants fail at an annual cost to Medicare of $90,000 compared to the less than $5000 annual cost to Medicare for the immunosuppressive drugs.

The Comprehensive Immunosuppressive Drug Coverage Act of 2013 would extend Medicare coverage for immunosuppressive drugs over a recipient’s lifetime—protecting Medicare’s investment in the transplant and ensuring that no patients will lose their kidney. As of press time, 16 senators and 116 representatives have signed onto the bill as co-sponsors.

Innovations in Kidney Research Congressional Briefing

In conjunction with Kidney Community Advocacy Day, ASN co-sponsored a standing-room only congressional briefing: “New Hope for Patients: Discussion of the latest cutting-edge breakthroughs in artificial kidney research.” Congressional Kidney Caucus Co-chairs Rep. Tom Marino (R-PA) and Rep. Jim McDermott (D-WA) served as honorary sponsors and spoke about their strong support for the kidney community and additional research funding to develop cures.

The following advocates, experts, and scientists also spoke at the briefing: William Fissell, Jonathan Himmelfarb, Shuvo Roy, Murray Sheldon, Robert Star, and Melanie Stewart.

“Currently kidney disease is the 8th leading cause of death in the U.S., affecting over 20 million Americans, and costing the federal government over $79 billion annually, including $34 billion for treatment of end stage renal disease. But it doesn’t have to be this way,” Dr. Himmelfarb said. “There are innovators, inventors, and scientists working now on transformative technologies that have the potential to make a fundamental difference for people living with kidney disease. Investing in research that spurs and supports innovation is the hope for the future.”

Summing up the day, ASN President Sharon Moe, MD, FASN, said: “It was a successful day by all accounts. More groups participated than ever before, more congressional offices were visited, and our new advocacy message was well received. I have been visiting offices for the past five years. It is clear that the kidney community is being heard and the voice of the American Society of Nephrology is well-respected.”

ASN is grateful to all who participated in Kidney Community Advocacy Day and will continue its efforts to engage Congress on these important legislative issues affecting patients with kidney disease.

Kevin F. Erickson, MD, and Mallika L. Mendu, MD, MBA, are ASN Public Policy Board Interns

Kidney Community Advocacy Day Participants

Alport Syndrome Foundation
American Association of Kidney Patients
American Kidney Fund
American Nephrology Nurses’ Association
American Society of Nephrology
American Society of Pediatric Nephrology
Dialysis Patent Citizens
Home Dialyzors United
IAGA Nephropathy Foundation of America
National Kidney Foundation
NephCure Foundation
PKD Foundation
Renal Physicians Association
Renal Support Network

ASN Public Policy Board Member Raymond Hakim, MD, PhD, (third from right) and Policy Board Intern Kevin Erickson, MD (right)
Can random UAC detect microalbuminuria in diabetic patients?

For microalbuminuria screening in patients with diabetes, measuring urinary albumin concentration (UAC) in random urine samples offers sensitivity and specificity similar to those of the albumin-to-creatinine ratio (ACR), reports a study in JAMA Internal Medicine.

A meta-analysis was performed with the use of data on 2078 patients from 14 studies evaluating UAC and ACR in random urine samples. All studies included 24-hour urine collections as the criterion standard for diagnosis of microalbuminuria.

In bivariate random-effects models, the two tests offered similar diagnostic performances. Pooled sensitivity in detecting microalbuminuria was 0.85 for UAC and 0.87 for ACR. Specificity was 0.88 for both tests; diagnostic odds ratios were similar as well. Performance was similar by timing of sample as well as on analysis of seven studies in which patients underwent both UAC and ACR.

Measuring ACR in random urine samples has some disadvantages as a screening test for microalbuminuria, including the higher cost of urinary creatinine measurement. Studies comparing ACR with UAC for this purpose have yielded conflicting results.

The new meta-analysis suggests that UAC and ACR have similarly good performances for microalbuminuria screening in diabetic patients. With the rising incidence of diabetes and limited health care resources in many countries, the authors conclude, “UAC of random urine samples may become the screening tool of choice for the population with DM” [Wu HY, et al. Diagnostic performance of random urine samples using albumin concentration vs ratio of albumin to creatinine for microalbuminuria screening in patients with diabetes mellitus: a systematic review and meta-analysis. JAMA Intern Med, published online May 05, 2014. doi:10.1001/jamainternmed.2014.1363].

Diabetes complications—rates are down, but numbers are still high

Although the incidence of diabetes-related complications in the United States has decreased since 1990, the burden remains high because of rising prevalence of diabetes, according to a report in the New England Journal of Medicine.

The researchers compiled nationwide data from multiple sources to assess trends in diabetes-related complications from 1990 to 2010. Age-standardized to the United States population in 2000, the data showed decreased incidence rates for all five complications of interest. Relative decreases were 67.8 percent for acute myocardial infarction, 64.4 percent for death resulting from hyperglycemic crisis, 52.7 percent for stroke, 51.4 percent for lower-extremity amputations, and 28.3 percent for ESRD.

When 1995 was used as the start year rather than 1990, the decline in ESRD was more similar to that for the other outcomes. Absolute declines in cases per 10,000 persons per year were 95.6 for myocardial infarction, 58.9 for stroke, 30.0 for lower-extremity amputation, 7.9 for ESRD, and 2.7 for death resulting from hyperglycemic crisis. However, once the rising prevalence of diabetes was taken into account, the reductions were significant only for myocardial infarction and death resulting from hyperglycemic crisis: by 32.2 and 42.0 percent, respectively. There was no significant change in the rates for amputation or stroke, and the ESRD rate increased by 90.9 percent: from 1.1 to 2.1 cases per 10,000 population.

The results suggest that improvements in preventive care have reduced the rates of important diabetes-related complications over the past two decades. However, as diabetes prevalence continues to rise, high numbers of complications persist nationwide. “The encouraging reductions in the rates of morbidity and hyperglycemia-related mortality in the population of adults with diabetes do not signify imminent reductions in the overall burden of diabetes-related complications,” the researchers conclude [Gregg EW, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med 2014; 370:1514–1523].

Fewer adults will receive BP drugs under JNCS

Under the 2014 BP guideline of the Eighth Joint National Committee (JNC8), antihypertensive therapy will be recommended for significantly fewer adults in the United States, reports a study in the Journal of the American Medical Association.

The researchers used data on 16,372 adults from the National Health and Nutrition Examination Survey between 2005 and 2010 to assess the implications of the JNC8 2014 BP guideline, compared with the previous JNC7 BP guideline. Among younger adults aged 18 to 59, the percentage for whom antihypertensive therapy would be recommended decreased from 20.3 percent under JNC7 to 19.2 percent under JNC8. The decrease was even sharper for those aged 60 or older: from 68.9 to 61.2 percent.

The 2014 blood pressure guideline was also associated with an increase in the proportion of treatment-eligible adults meeting blood pressure targets: from 41.2 to 47.5 percent in those aged 18 to 59 and from 47.5 to 65.8 percent in those aged 60 or older. Overall, 1.6 percent of adults aged 18 to 59 and 27.6 percent of those aged 60 or older were receiving antihypertensive drugs and meeting more stringent JNC7 targets. Under JNC8, some of these patients would be eligible for less stringent or no BP therapy.

The JNC8 guideline increased the systolic BP treatment goal from less than 140/90 to less than 130/80 mm Hg while increasing the target for patients with chronic kidney disease and diabetes from less than 130/80 to less than 140/90 mm Hg. The new study suggests that in comparison with JNC7, antihypertensive therapy will be recommended for fewer Americans under JNCS.

Under JNCS, more patients will be considered to have met BP targets, especially in those aged 60 and over. More study is needed to determine how the new guideline will affect overall BP levels and the resulting effects on cardiovascular disease outcomes [Navar-Boggan AM, et al. Proportion of US adults potentially affected by the 2014 hypertension guideline. JAMA 2014; 311:1424–1429].

Little benefit of spironolactone for heart failure with preserved ejection fraction

Treatment with spironolactone doesn’t improve overall outcomes for heart failure patients with preserved left ventricular function, reports a trial in the New England Journal of Medicine.

The Study of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial included 3445 patients with symptomatic heart failure but an ejection fraction of 45 percent or higher. They were randomly assigned to double-blinded treatment with spironolactone, 15 to 45 mg/d, or placebo, added to existing therapy. A composite outcome of death resulting from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure was assessed at a mean follow-up time of 3.3 years.

A primary outcome event occurred in 18.6 percent of patients receiving spironolactone and 20.4 percent with placebo. The difference was not significant: incidence rates were 5.9 and 6.6 events per 100 person-years, respectively. The rate of hospitalization for heart failure was lower in the spironolactone group: 12.0 versus 14.2 percent, hazard ratio 0.83.

The rates of all-cause mortality and hospitalization were also similar between groups. Patients receiving spironolactone had higher rates of increased serum creatinine and hyperkalemia but a lower rate of hypokalemia. There were no differences in serious adverse events, including serum creatinine of 3.0 mg/dL or higher or dialysis. The authors note that the study protocol included frequent patient monitoring.

For patients with heart failure and left ventricular dysfunction, mineralocorticoid-receptor antagonists reduce the risk of death and heart failure hospitalization. Some studies have reported that these drugs improve diastolic function in heart failure patients with preserved ejection fraction. However, the TOPCAT trial found no overall reduction in cardiovascular outcomes with spironolactone added to existing therapy in this group of patients. The results suggest some reduction in hospitalization for heart failure in patients treated with spironolactone. In treated patients, close monitoring is warranted because of the heightened risk of hyperkalemia and increased creatinine levels [Pitt B, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014; 370:1383–1392].
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Kidney News

CME/BE NEPHROLOGIST
Outstanding opportunity for full-time, CME/BE Nephrologist in a Single Specialty Practice. The physician will join six FT nephrologists and two non-physician providers in a well-established, physician-owned practice that began operation in 1980. The Nephrologist will work in an excellent, award-winning medical community and support patients in eight dialysis units. The compensation package is competitive with paid medical/dental benefits for physician and family, generous 401k plan, and paid malpractice insurance. There is a two year partnership track that includes a JV opportunity. A signing bonus is included in the first year salary. There will be time to enjoy Colorado with a four day work week, one call weekend per month and six weeks of annual vacation. Fort Collins is located in northern Colorado, an hour north of Denver. The city is 5000 feet above sea level and enjoys 300 days of sunshine and only 14.5 inches of precipitation a year. Fort Collins is home to Colorado State University and an outstanding public school system. Fort Collins is not in an underserved area. Send CVs to thenephrologyclinic@gmail.com or fax to 970-493-2682.

CHIEF, DIVISION OF NEPHROLOGY
Newton-Wellesley Hospital (NWH), a community teaching hospital in suburban Boston and a member of the Partners HealthCare System, Inc. (founded by the Massachusetts General Hospital (MGH) and the Brigham and Women’s Hospital), seeks a clinical nephrologist who demonstrates excellence in patient care, teaching, and administration, to serve as Chief of the Division of Nephrology. This individual, who will practice nephrology at NWH while overseeing the division, will identify opportunities to grow and expand the division. NWH is home to a comprehensive Cancer Center and is developing a state-of-the-art noninvasive Cardiovascular Center, in collaboration with MGH. NWH is an affiliate of the Tufts University School of Medicine and has postgraduate training programs for both Harvard Medical School and Tufts University School of Medicine trainees. The candidate must be Board Certified in Nephrology and qualify for an academic appointment at the rank of clinical associate professor or clinical professor. Please send cover letter and CV to Lawrence S. Friedman, MD, Chair, Department of Medicine, Attn: Alison Sholock, Newton-Wellesley Hospital, 2014 Washington Street, Newton, MA 02462, FAX 617-243-6701, Email asholock@partners.org. NWH is an equal employment opportunity employer.

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These plus more opportunities available when you contact
Rhonda Truitt
rhonda.truitt@wt-group.com
443-512-8899 x 106
Phoslyra® (calcium acetate oral solution, 667 mg per 5 mL) is a phosphate binder (PB) indicated for the reduction of serum phosphorus in patients with end stage renal disease (ESRD). Phoslyra is administered orally with meals.

INDICATIONS AND USAGE: Phoslyra® sodium acetate oral solution 667 mg per 5 mL is a phosphate binder indicated to reduce serum phosphorus in patients with end stage renal disease (ESRD), Management of elevated serum phosphorus levels usually includes all of the following: reduction in dietary intake of phosphorus, removal of phosphorus by dialysis, and inhibition of intestinal phosphaturic acid secretion with phosphate binders.

DOSAGE AND ADMINISTRATION: The recommended initial dose of Phoslyra to the adult dialysis patient is 10 mL with each meal. Increase the dose gradually to a level of serum phosphorus levels in the target range, as long as hypercalcemia does not develop. Titrate the dose every 2 to 3 weeks until an acceptable serum phosphorus level is reached. Most patients require 15–20 mL with each meal.

CONTRAINDICATIONS: Patients with hypercalcemia.

WARNINGS AND PRECAUTIONS:

Hypercalcemia: Patients with end stage renal disease may develop hypercalcemia when treated with calcium-containing sodium acetate. Phoslyra, like the cornerstone use of sodium supplements, including calcium-based bone health products, with Phoslyra overuse of Phoslyra may lead to progressive hypercalcemia and may result in bone and muscle dysfunction, and renal, or cardiac function, and of concomitant disease or other drug therapy.

IMPORTANT SAFETY INFORMATION:

• Phoslyra may cause diarrhea with nutritional supplements that contain maltitol.

• There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of the medication would have a clinically significant effect on its safety or efficacy, administer the drug one hour before or three hours after Phoslyra or calcium acetate. This is also recommended for concomitant drugs that have a narrow therapeutic range. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizures are not generally recommended to take concomitant drugs that have a narrow therapeutic range of Phoslyra. Seizures with anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizures are not considered to have a clinically significant effect on the safety or efficacy of Phoslyra.

• Concomitant Use with Medications. Hypercalcemia may aggravate digitalis toxicity; these patients should be closely monitored when digitalis preparations are used. The serum level is reached. Most patients require 15–20 mL with each meal. Serum phosphorus levels to the target range, as long as hypercalcemia does not develop. Titrate the dose every 2 to 3 weeks until an acceptable serum phosphorus level is reached. Most patients require 15–20 mL with each meal.

Table 1: Adverse Reactions in Patients with End Stage Renal Disease

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Total adverse reactions reported for calcium acetate oral solution (N=478)</th>
<th>3-mo, open-label study of calcium acetate oral solution (N=25)</th>
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<th>3-mo, open-label study of calcium acetate oral solution (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocalcemia</td>
<td>22 (2.3)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Phosphaturia</td>
<td>21 (2.3)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19 (2.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (2.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (1.8)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
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<tr>
<td>Flatulence</td>
<td>16 (1.7)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (1.5)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
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<tr>
<td>Dry mouth</td>
<td>13 (1.4)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
<td>1 (0.0)</td>
</tr>
</tbody>
</table>

In patients with ESRD...

First and only FDA-approved little LIQUID phosphate binder

• May lessen pill burden
• Potential to reduce optional fluid intake associated with administration of solid PBs
• No water required
• Premixed—No need to reconstitute or dissolve in water
• No refrigeration, even after opening

For additional important safety information, please see brief Prescribing Information on this page.

Fresenius Medical Care

For more information on Phoslyra, please contact Fresenius Medical Care NA at 800-323-5188. Manufactured for and distributed by Fresenius Medical Care, Waltham, MA 02451. Fresenius Medical Care and Phoslyra are trademarks of Fresenius Medical Care Holdings, Inc. or its affiliates company. All other trademarks are the property of their respective owners. ©2012 Fresenius Medical Care NA.

101733-02 Rev. A 08/2012