The Development of Urinary Biomarkers for Kidney Disease: Is the Search for Our Renal Troponin

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The practice of nephrology is long recognized to treat and
comfort on the basis of a blend of science and art. As nephrolo-
gists, we do an amazing job of monitoring kidney function
with rather rudimentary measures such as serum creatinine
and urine output. When patients ask what are the “normal”
values for each of these measures, we all answer in a similar and
somewhat nonspecific manner reflecting the “art” of interpre-
tation: What is normal creatinine? Answer: It is like golf: High
is bad, low is good. What is a normal amount of urine? Answer:
Depends on how much you drank and ate.

The new field of biomarkers for kidney injury or disease is an
exciting and rapidly advancing scientific area. Recent develop-
ments in the study of several urinary biomarkers of kidney injury
have focused on NGAL, NAG, and KIM-1. Two articles in this
issue of JASN are part of a growing literature that will shift the
balance between the art and science of understanding—shifting
toward new evidence that anticipates changes in kidney function
more reflective of better science.1,2 As we read this rapidly growing
literature and seek out our “renal troponin,” we can take a lesson
from our cardiology colleagues: Our ultimate goal is to identify
patients with a clinical syndrome earlier to initiate promptly a
therapy that ultimately affects outcomes in a more positive way. It
is these last two points that will be essential in prioritizing our
future research agenda.

The new study by Siew et al.1 provides data to support the use
of urinary NGAL as a predictor of acute kidney injury (AKI) in the
intensive care unit. More than 400 critically ill patients in intensive care were enrolled, had urinary NGAL measured, and
were followed prospectively to identify those with AKI defined as an increase in serum creatinine of >0.3
mg/dl or 50%. Median values of urinary NGAL were significa-
cantly higher on enrollment in patients who experienced AKI
than those with HIV without AKI.1 Furthermore, it is clear that considerable over-
lap exists in the ranges of NGAL for groups with and without
AKI.1

The new study by Paragas et al.2 also provides data to sup-
port the ability of urinary NGAL to discriminate among different
types of kidney disease in patients with HIV infection. Pa-
tients with HIV-associated nephropathy had significantly
greater values of urinary NGAL than those with HIV without
chronic kidney Disease (CKD), those with HIV and CKD (not
HIV-associated nephropathy), and those with a variety of non-
HIV glomerular lesions. The choice of multiple comparison
groups allows the reader to consider the effect of HIV infec-
tion, CKD, both, or neither and the multiple types of kidney
diseases in relation to the level of urinary NGAL.

Although these new studies will play a foundation role in
the future validation of these biomarkers, they are not without
limitations. Minor methodologic issues can be discussed, such
as the use of a dichotomized outcome of AKI. Although the
definition is widely accepted and common in the literature,
arguably, AKI exists on an exaggerated spectrum from the
damage of a single tubular cell to acute cortical necrosis. Un-
derscoring this continuum is a recent article examining NGAL
and other urinary biomarkers after cardiac surgery.3 In that
study, regardless of whether the patient was considered to have
or have not experienced AKI (using the same definitions used
by Siew et al.1), a rise from the baseline value with subsequent
fall back to baseline was seen over time. Stated another way,
even patients without any significant change in creatinine ex-
perienced a rise and fall in their urinary NGAL. In the study in
this issue of JASN, there were also statistical differences in mean peak concentrations of NGAL between those with and
without AKI.1 Furthermore, it is clear that considerable over-
lap exists in the ranges of NGAL for groups with and without


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AKI. This strongly suggests that considerably milder degrees of AKI, including those that cannot be detected with serum creatinine, may result in a rise in NGAL. This overlap is also present in the article by Paragas et al.,

The second application, as explored in the article by Paragas et al., may have a more immediate impact. Our ability to differentiate between particular histologic lesions using urine studies rather than biopsy will represent a major leap ahead in the early detection of acute kidney injury after cardiac surgery. Clin J Am Soc Nephrol 20: 873–882, 2009

The development of strategies to treat AKI more actively and successfully will soon follow the discovery of how to diagnose AKI earlier and earlier.

Before we adopt these biomarkers in such a role, we must not forget that these urine studies are actually intermediate tests triggered. Finally, we need to prioritize studies in which treatment of the patient will be affected and early knowledge of the disease or injury will benefit outcome. Hopefully, the development of strategies to treat AKI more actively and successfully will soon follow the discovery of how to diagnose AKI earlier and earlier.

The second application, as explored in the article by Paragas et al., may have a more immediate impact. Our ability to differentiate between particular histologic lesions using urine studies rather than biopsy will represent a major leap ahead in the early initiation of therapy for CKD. Our subsequent ability to follow disease activity and success of treatment using these biomarkers rather than urine sediment or serial biopsies will also need to be demonstrated, and when that time comes, there will be a major advantage in the monitoring and modulation of therapies.

Before we adopt these biomarkers in such a role, we must not forget that these urine studies are actually intermediate outcomes. They will need to be validated in the rigorous manner as outlined by the McMaster criteria. Although they clearly correlate with the event of interest, we must further understand how a change in their measure represents a change in the event under study. This may seem a daunting task, but if the cardiologists can do it with troponins, then so can we.

DISCLOSURES
None.

REFERENCES


Does Idiopathic Hypercalciuria Trigger Calcium-Sensing Receptor–Mediated Protection from Urinary Supersaturation?

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Kidney stone formation is common, affecting 5 to 6% of the American adult population, and highly recurrent. Approximately 70% of stones are composed predominantly of calcium oxalate (CaOx) with small amounts of calcium phosphate (CaP); another 10% are largely CaP. The physicochemical requirement for stone formation is supersaturation of urine with respect to the stone minerals. In the case of calcium stones, supersaturation is driven by urine calcium concentration, which is a function of calcium excretion and urine volume. For CaP, supersaturation is also controlled by urine pH, because solubility of this salt decreases as urine pH rises; CaP stones are seen largely in patients with urine pH >6.

Biopsies of renal medullary papillae of stone formers, taken during percutaneous nephrolithotomy, demonstrate that stone formers are also characterized by specific patterns of mineral deposition in tissue. Common idiopathic CaOx stone formers have interstitial deposits of CaP in the medullary interstitium, so-called Randall’s plaques, which begin in the thin loops of Henle and extend downward toward the base of the renal tubule.