et al.\textsuperscript{14} are closely in line with previously published work from the same group and are supported by other works on IRI.\textsuperscript{12,13}

Clearly, it is important to consider what relevance this study may hold for human health. The US experimental strategy carried out by Gigiotti et al.\textsuperscript{14} in the mice is readily feasible in human subjects and does not involve the use of a pharmacological agent. Indeed, many cholinergic pharmacological agonists exhibit a narrow therapeutic index, limiting their clinical use. Importantly, the noninvasive US regimen relies on US settings within approved Food and Drug Administration guidelines. Opportunities arising from the work by Gigiotti et al.\textsuperscript{14} are numerous and promising, because many procedures that carry a very high risk of AKI, such as cardiac surgery with cardiopulmonary bypass, iodinated contrast intravenous injection, or renal conditioning, are planned before transplantation. In renal transplantation, enhanced IRI significantly contributes to delayed graft function, which affects the future of the transplanted organ.\textsuperscript{15} Moreover, brain death is associated with the termination of the CAP, which significantly contributes to premortem systemic inflammation and worsening of IRI in potential transplanted end organs.\textsuperscript{16} Other nonrenal diseases could be modulated through CAP stimulation (e.g., myocardial ischemia, hepatic injury, sepsis, and endotoxemia), significantly expanding the potential range of application of this method. Finally, in searching for novel approaches to prevent and even cure AKI, we believe that splenic US stimulation has a bright future ahead.

DISCLOSURES

None.

REFERENCES


Galectin-3 and New-Onset CKD: Marker or Mediator?

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In the last 2 decades, the number of PubMed citations including the term biomarker or marker has increased exponentially by 8.6% additional citations per year, from 9863 citations in 1992

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to 55,190 in 2012. The number of citations in nephrology has increased by 9.7% per year, from 576 in 1992 to 3931 in 2012. These studies examined diverse biologic clues, involving changes in blood, urine, or body tissues of the levels or expression of small molecules, proteins, enzymes, DNA, RNA, and antibodies. The goals varied, but included attempts to gain insight into disease mechanisms, to develop new screening, diagnostic, or treatment strategies, to assess the efficacy of interventions, or to identify cases more likely to respond to treatment or with worse prognosis.

This hectic hunt for the next promising biomarker is fueled by the need for more reliable tools to inform clinical decision making and health policy. In fact, in several medical disciplines, including nephrology, disease cases are identified too late to fully benefit from interventions of proven efficacy or referral to specialist clinics. For example, guidelines recommend early recognition of CKD and risk assessment, because timely implementation of some available therapies can slow disease progression and reduce the incidence of cardiovascular complications. However, people with CKD are commonly referred to nephrologists late, usually when the estimated GFR (eGFR) is <30 ml/min per 1.73 m². Case classification improvement resulting from the inclusion of proteinuria in addition to eGFR within the new CKD classification system suggests that combinations (panels) of biomarkers (biomarker “signatures”) may be more useful than single-molecule indicators. However, the quest for new biomarkers may take several years, might cost hundreds of millions of dollars, and may never translate into helpful clinical tools.

In this issue of the *JASN*, O’Seaghdha et al.° report data on galectin-3, a soluble β-galactoside-binding lectin highly expressed in monocytes, which plays important regulatory roles in inflammation, immunity, and cancer, and may be involved in the pathogenesis of atherosclerosis, diabetes, and asthma. Interest in galectin-3 is justified by its profibrotic properties. Galectin-3 has been shown to promote TGF-β–mediated activation of fibroblasts into matrix-secreting myofibroblasts in liver and renal tissues. In hypertrophied hearts, galectin-3 is upregulated and has a stimulatory effect on macrophage migration, fibroblast proliferation, and development of fibrosis. Higher levels of galectin-3 have been linked to reduced eGFR in cross-sectional studies, new-onset heart failure in Framingham Offspring participants, and mortality in subjects with heart failure. Because the liver primarily excretes galectin-3, elevations of its levels before overt kidney disease would potentially make it a useful biomarker to identify people at risk for CKD (e.g., those with diabetes or hypertension). O’Seaghdha et al.° hypothesized that galectin-3 may predict new-onset CKD and progression of CKD in the general population, and studied the association of galectin-3 measured at examination 6 (1995–1998) in 2450 Framingham Offspring participants with follow-up data at examination 8 (2005–2008). Consistent with the study hypothesis, galectin-3 predicted rapid decline in eGFR (23 ml/min per 1.73 m² per year) and new-onset CKD (eGFR <60 ml/min per 1.73 m²), but not development of albuminuria (albumin/creatinine ratio ≥17 mg/g for men or ≥25 mg/g for women).

This study is important for several reasons. First, it is the first relatively large longitudinal population-based study reporting data on the relationship between galectin-3 measured at baseline in a cohort of people with normal kidney function and distant clinical outcomes, including objective measures of CKD. This temporality criterion is key to identifying exposure-disease relationships that are potentially causal in nature. Participants were assembled using prespecified criteria and follow-up was relatively complete. Robustness of findings in adjusted analyses (including age) and treating galectin-3 as either a continuous or categorical variable supports the observed association and suggests the existence of a biologic gradient. Second, the relationship is biologically plausible. CKD progression is characterized by development of tubulointerstitial fibrosis and galectin-3 is a proven profibrotic mediator, including in renal tissues. On the other hand, lack of association between galectin-3 and occurrence of albuminuria suggests that this biomarker predicts tubulointerstitial fibrosis but not glomerular injury. Finally, the findings from this epidemiologic study are coherent with those from *in vitro* and animal models, and analogous to those from studies in patients with diabetes and cardiovascular disease.

Although promising, the associations found in this study between levels of galectin-3 and distant renal events need to be confirmed in different populations and settings to be generalizable. The relatively weak associations described (i.e., 50% risk increase per SD of log-galectin-3 concentration and relatively low measures of net reclassification improvement) do not exclude its potential role in a panel of prognostic biomarkers. However, they reduce its appeal as diagnostic (screening) marker considering that very high degrees of association (i.e., odds ratios >80) are necessary if a biomarker-based test is to yield >90% sensitivity and specificity ([0.9/0.1]/[0.1/0.9] = 81). More importantly, the prognostic ability of galectin-3 needs to be confirmed in prognostic studies including internal derivation and external validation samples and ultimately randomized controlled trials testing the role of the addition of this new test (or a panel including galectin-3) to data currently used for this purpose, including history, physical examination, and assessment of albuminuria and eGFR trajectories. The new marker or panel would then be assessed in a Bayesian way for its incremental knowledge adding properties. Such studies would consider whether results are consistent across different laboratories as well as whether physicians can correctly interpret findings and use them to make treatment decisions. Finally, whether galectin-3 is a disease mediator rather simply a marker of disease can be tested with intervention studies looking at treatments with the potential to attenuate the profibrotic effects of galectin-3.

In summary, galectin-3 may be causally involved in mechanisms of tubulointerstitial fibrosis and CKD progression, and it is easily measurable and independently associated with renal end-points. Although galectin-3 may not be used as a
diagnostic biomarker, further studies may show stronger associations with clinical end-points (i.e., greater odds ratios of highest versus lowest percentiles of galectin-3 levels) in people at risk. Validation studies and clinical trials are required to establish whether galectin-3 can be considered a useful prognostic marker or a mediator of kidney fibrosis and progressive CKD, and therefore a target of new therapies to reduce the risk of end stage kidney failure.

DISCLOSURES
None.

REFERENCES


APOL1 and Progression of Nondiabetic Nephropathy

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African Americans are disproportionately affected by most common causes of nephropathy and develop ESRD at rates approximately 3.5 times higher than those in European Americans.1 Population ancestry-based disparities in nondiabetic nephropathy have recently been attributed to two variants in the C-terminal domain of the apolipoprotein L1 gene (APOL1) on chromosome 22—G1: rs73885319 and rs60910145, encoding two highly correlated nonsynonymous amino acid changes, and G2: rs71785313, a two–amino acid deletion.2 These alleles are nearly absent in populations of Americans.1 Population ancestry-based disparities in nondiabetic nephropathy at rates approximately 3.5 times higher than those in European Americans.