Progression after AKI: Understanding Maladaptive Repair Processes to Predict and Identify Therapeutic Treatments


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ABSTRACT

Recent clinical studies indicate a strong link between AKI and progression of CKD. The increasing prevalence of AKI must compel the nephrology community to consider the long-term ramifications of this syndrome. Considerable gaps in knowledge exist regarding the connection between AKI and CKD. The 13th Acute Dialysis Quality Initiative meeting entitled “Therapeutic Targets of Human Acute Kidney Injury: Harmonizing Human and Experimental Animal Acute Kidney Injury” convened in April of 2014 and assigned a working group to focus on issues related to progression after AKI. This article provides a summary of the key conclusions and recommendations of the group, including an emphasis on terminology related to injury and repair processes for both clinical and preclinical studies, elucidation of pathophysiologic alterations of AKI, identification of potential treatment strategies, identification of patients predisposed to progression, and potential management strategies.


AKI remains a significant health burden that is characterized by high initial mortality, morbidity, and substantial effect on health care costs. Recovery in surviving patients depends on the reversal of hemodynamic impairment, removal of nephrotoxin exposure, and successful repair of the renal parenchyma. The recovery process has generally been considered to be efficient, and the traditional view has been that surviving patients will suffer no long-term renal effects. Although several small single-center studies suggested that patients who survive AKI have varying levels of renal recovery predisposing them to CKD and ESRD, these studies applied varying criteria for both AKI and follow-up times to identify injury progression. Because of the limited scope of these studies, speculation on a causative link between AKI and CKD was not appreciated, resulting in no real change in management or outcomes of patients after AKI.

Over the last decade, there has been a dramatic increase in research on the chronic sequelae of AKI. Using AKI or ARF combined with CKD or fibrosis and human as search terms, a PubMed search identified an average of 135 papers annually from 2009 to 2013 versus approximately 22 papers annually from 1999 to 2003. Notable studies have used large government or private insurance databases and found significant correlations between episodes of AKI and progression to CKD and ESRD. A recent meta-analysis found an 8.8-fold increase in risk for CKD and a 3.3-fold increase in risk for ESRD in patients surviving AKI after hospital discharge. Therefore, recent clinical data implicates AKI as a significant risk factor for CKD progression and ESRD.
It is now clear that these recent developments present the nephrology community with a new set of challenges and questions regarding the link between AKI and CKD. Indeed, despite the strong connection, practical questions regarding how to define and identify patients who are most susceptible to progression and the underlying pathophysiologic mechanisms leading to decline remain to be answered. Given these considerations, a working group of the 13th Acute Dialysis Quality Initiative (ADQI) Conference sought to address the following five questions of broad interest to the nephrology community regarding AKI and progression.

(1) How do we define progression after AKI?

(2) What is known about the pathophysiologic mechanisms of progression after AKI?

(3) What are the relevant biochemical pathways related to progression that might lend themselves to therapies?

(4) Can progression to CKD be predicted after AKI, and can the key risk factors be identified?

(5) What are the best treatment strategies to prevent or limit progression?

METHODS

The 13th ADQI Consensus Conference on Therapeutic Targets of Human AKI held in Charlottesville, Virginia in April of 2014 (www.adqi.net) was attended by an international group of experts and focused on an objective scientific review of the current literature, developing a consensus of opinion, with evidence where possible, to distill current literature and articulate a research agenda to address important unanswered questions. Similar to other ADQI meetings, a modified Delphi approach was followed. Details of the methods can be found in the supplement of the introduction and summary by Okusa et al. in the introduction to the series in this issue of the Journal of the American Society of Nephrology.

RESULTS

Question 1. How Do We Define Progression after AKI?

Consensus statement: Precise and unambiguous terminology should be adopted to describe both the continuing functional deterioration and structural damage that persist in the kidney after acute injury.

AKI represents the end result of a series of biologic processes that occur after the initial insult and a subsequent host response. Several preclinical studies in different models of AKI have elucidated the injury and repair mechanisms that contribute to the eventual outcome.6–8 Although the optimal outcome is complete resolution of normal structure and function, this is often not the case, and repair may be incomplete or imperfect. Greater clarity is necessary in the terminology used to accurately describe the dynamic nature of these processes. Consensus on a set of definitions (Table 1) that could be applied across the preclinical and clinical spectrum of AKI was developed.

The clinical course of AKI can be considered in three phases. The development phase represents the immediate effects of the insult, in which the GFR can be compensated for by the underlying renal reserve, resulting in limited clinical or biochemical (as currently measured through changes in serum creatinine) signs of damage or functional change. This phase may be clinically silent and only detected through sensitive kidney injury-specific biomarkers. In the extension phase, evidence of damage and functional change becomes apparent and represents both the injury and repair mechanisms in play. Current definitions of AKI rely on changes in functional markers, such as creatinine and urine output, to identify AKI, and they have generally lacked the precision to distinguish the development, extension, and resolution phases after an injury. However, emerging biomarkers of kidney damage, such as neutrophil gelatinase–associated lipocalin, kidney injury molecule-1 (KIM-1), IL-18, tissue inhibitor of metalloproteinases-2, and IGF binding protein 7, provide an opportunity to further characterize AKI. As described in a recent ADQI conference6,8 the combined use of functional and damage biomarkers can be used to recognize whether the renal insult has resulted in changes in injury biomarkers alone, functional changes alone, or both. If the injury is severe enough, the extension phase may result in the need for temporary or permanent dialysis. The resolution phase represents the net result of the injury and repair mechanisms, and the clinical course is influenced by the nature and severity of AKI, its duration, and the frequency of repeat episodes.

Figure 1 illustrates the consequences of a renal insult on the subsequent recovery response. After an insult, an admixture of the injury mechanisms with adaptive and maladaptive repair processes will determine the measurable elements of kidney structure and function. Repair and injury mechanisms are initiated nearly simultaneously, and the ability to contain and repair damage and restore normal structure is a key function of kidney reparative potential. Normal kidneys have the ability to modulate GFR and other renal functions in response to increased demand to maintain homeostasis when exposed to stresses. This renal reserve has largely been identified through changes in GFR after a protein or amino acid load, and it is influenced by age, comorbidities, and the underlying disease states contributing to renal injury.9 It is expected that renal reserve would buffer the change in GFR in response to any injurious stimuli and may compensate for a mild injury that results in elevations in some damage biomarkers, preventing detectable functional change (e.g., in serum creatinine) (Figure 1A). In Figure 1B, injury is severe enough to result in clinically detectable AKI with repair mechanisms that keep pace with the injury, resulting in functional resolution...
Table 1. Proposed definitions for terms related to events mediating resolution or progression after AKI

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Hallmarks</th>
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<tbody>
<tr>
<td>Repair</td>
<td>A mechanistic process initiated rapidly in response to injury, success of which depends on microenvironmental factors</td>
<td>Process starts concurrently after an insult; however, timing, magnitude, and duration are conditioned by host factors</td>
</tr>
<tr>
<td>Adaptive repair</td>
<td>Resolution of renal structure free of long-term sequelae (normal structure and function at 90 d)</td>
<td>Rapid return of renal function; tubular proliferation and resolution of pathology and inflammation; decrease in damage biomarkers</td>
</tr>
<tr>
<td>Maladaptive repair</td>
<td>Process that results in a durable reduction in kidney function usually associated with change in renal structure</td>
<td>Persistence of renal dysfunction; development of fibrosis; persistent expression of profibrogenic factors; delayed resolution of inflammation or markers of inflammation and damage markers</td>
</tr>
<tr>
<td>Recovery</td>
<td>A consequence of repair that leads to durable improvement in kidney function and/or structure; can be partial or complete</td>
<td>Parameters would include GFR, tubular function, hormonal components, metabolic components, markers of injury, etc.; patterns of recovery may differentiate among parameters; quality and quantity of recovery can be assessed by biomarkers, imaging, and histopathology</td>
</tr>
<tr>
<td>Progression</td>
<td>Durable change in structure or function</td>
<td>Persistent abnormalities in structure or function detected by biomarkers, imaging, or histopathology</td>
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during time. In either Figure 1A or Figure 1B, maladaptive repair may surpass the capacity of compromised renal reserve, resulting in the functional manifestation of CKD over time. In Figure 1, C and D, AKI is superimposed on CKD with minimal reserve, and limited adaptive repair is unable to restore function, whereas maladaptive repair predisposes to fibrosis and CKD. The hallmark for progression is the development of fibrosis and scarring that reduces renal functional mass, and therefore, it should be defined within the context of the tissue’s capacity to restore functional or structural impairment.

Although experimental models for AKI have identified factors that influence adaptive and maladaptive repair after AKI (Table 2), there is a paucity of data in clinical AKI. This is partly related to the lack of prospective longitudinal cohort studies of patients after AKI who have been assessed for specific kidney damage, progression to CKD, and functional biomarkers. Some prospective studies have suggested a link between biomarker expression and progression after AKI, whereas additional prospective studies are underway, which may provide needed information. To what extent renal reserve mitigates the effects of renal injury in humans is also not well studied and will require further investigation.

Question 2. What Is Known about the Pathophysiologic Mechanisms of Progression after AKI?

Consensus statement: Maladaptive repair occurs in the tubular, vascular, and interstitial compartments in response to AKI, predisposing to development of interstitial fibrosis.

Both human and animal studies have shown that a variety of intrinsic repair processes are activated rapidly after kidney injury. Sustained recovery might be attributed to adaptive repair, whereas progression results directly or secondary to maladaptive repair processes. Several pathophysiologic processes constitute maladaptive repair with the potential to promote interstitial fibrosis. For example, a reduction in capillary density after AKI may exacerbate renal hypoxia and thus, promote interstitial fibrosis. There is also an expansion of interstitial fibroblasts and myofibroblasts in different models of AKI. Although the origin of these cells is debated, such cells may result from pericyte activation to a myofibroblast-like state or phenotypic transition of endothelial cells to produce interstitial fibroblasts. Epithelial-mesenchymal transition resulting in transdifferentiation of epithelial cells to myofibroblasts is not found in some models of AKI but has been reported in others (e.g., ureteral obstruction).

The expansion or maintenance of injury–induced interstitial changes may be driven by additional paracrine cues derived from the local injury/repair environment. Profibrotic factors (e.g., TGF-β, connective tissue growth factor, and platelet–derived growth factor-B) are produced by tubular epithelial cells and infiltrating cells, such as macrophages or lymphocytes. Maladaptive repair of tubular cells may occur when epithelial cells fail to fully redifferentiate or become growth arrested in G2; these cells represent an additional source of profibrotic factors.

We have defined maladaptive repair as a process that results in a durable reduction in kidney function usually associated with change in renal structure (Table 1) and emphasize that such alterations represent a necessary but not sufficient ingredient to promote progression. As pointed out recently by Venkatachalam et al., interstitial fibrosis is not necessarily self-perpetuating and indeed, may subserve an important function, such as protecting undamaged regions from damaged parenchyma...
to limit the severity of injury. Although interstitial scaring may not be directly progressive in nature, it likely predisposes to exaggerated responses to secondary injury, reduces renal functional reserve, and contributes to the development of hypertension.4,26

Table 2 summarizes the animal models used to date to evaluate the pathophysiologic events of AKI resulting in CKD. Most models have used ischemia-reperfusion (I/R) in either rats or mice combined with histologic or biochemical evidence of fibrosis as a primary end point. Other functional end points, such as proteinuria and hypertension, are easily assessed in rats but not mice. Reduced renal mass or dietary manipulations can influence the speed and magnitude of fibrosis, and such maneuvers may provide insight into unique mechanisms driving

Figure 1. Conceptual illustration of events after a renal insult. The ongoing events of injury and repair represent possible scenarios in which the degree of injury and established repair potential contribute to resolution or progression, with red lines indicating the injury and green lines representing repair activity. (A) Subclinical AKI with adaptive repair, in which injury reaches threshold levels of damage markers (i.e., KIM-1) but is lower than functional markers (i.e., changes in creatinine). Repair matches the injury, resulting in adaptive repair. (B) A greater level of injury increases both damage and functional markers, resulting in clinical AKI, and repair activity matches injury, leading to complete resolution. (C) Repair activity is overwhelmed by injury, and fibrosis develops (orange), leading to chronic damage and nonrecovery with higher levels of damage and functional markers than at the start. (D) The development of two episodes of injury superimposed on underlying CKD, with the biomarker levels starting above the threshold of significance. As the first injury is being repaired, there is a second insult, which occurs before completion of repair. The two shades of orange and brown represent the contributions of the original injury and the second insult, respectively, toward maladaptive repair and fibrosis. The fibrotic response is exacerbated, because repair mechanisms are already exhausted, and additional injury results in greater separation between the two processes. The horizontal line at which the repair ends is much higher than the start, representing the decrease in function and a higher creatinine level.
Table 2. Summary of animal models used to investigate the pathophysiology of progression after AKI

<table>
<thead>
<tr>
<th>Species</th>
<th>Method</th>
<th>Time Point</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male CS7BL/6J or Ve-Cadherin-Red Rosa reporter mice (8–10 wk old)</td>
<td>Bilateral ischemia (28 min, 36.5°C–37.5°C)</td>
<td>Day 56</td>
<td>Fibrosis and capillary rarefaction</td>
<td>15</td>
</tr>
<tr>
<td>Male CS7BL/6Jei × C3H/HeSnJ mice (6–8 wk old)</td>
<td>Unilateral ischemia (45 min, 37°C)</td>
<td>Day 28</td>
<td>Fibrosis</td>
<td>71</td>
</tr>
<tr>
<td>Male BALB/c mice (8 wk old)</td>
<td>Bilateral ischemia (30 min)</td>
<td>Day 21</td>
<td>Fibrosis and inflammation</td>
<td>34</td>
</tr>
<tr>
<td>Male BALB/c mice (8–10 wk old)</td>
<td>Bilateral ischemia (30 min, 37.0°C; moderate IRI or 32 min, 37.5°C; severe IRI) or unilateral ischemia (30 min, 37°C)</td>
<td>Day 42</td>
<td>Fibrosis</td>
<td>31</td>
</tr>
<tr>
<td>Male BALB/c mice (8–10 wk old)</td>
<td>Unilateral ischemia (30 min, 37°C)</td>
<td>Day 14</td>
<td>Fibrosis</td>
<td>24</td>
</tr>
<tr>
<td>Male CD-1 mice (30–45 g)</td>
<td>Bilateral I/R</td>
<td>Day 14</td>
<td>Fibrosis</td>
<td>72</td>
</tr>
<tr>
<td>Male CD-1 mice (35–45 g)</td>
<td>Bilateral ischemia (30 min, 37°C)</td>
<td>Days 7 and 21</td>
<td>Fibrosis, capillary rarefaction, hypertension</td>
<td>16</td>
</tr>
<tr>
<td>Male Sprague–Dawley rats</td>
<td>Left unilateral ischemia (40 min, 37°C) 2 wk after right uninephrectomy and surgical excision of both poles of the left kidney (75% reduction of renal mass) or right uninephrectomy (50% reduction of renal mass)</td>
<td>Day 28</td>
<td>Fibrosis, capillary rarefaction, hypertension</td>
<td>74</td>
</tr>
<tr>
<td>Male Sprague–Dawley rats (6–8 wk old)</td>
<td>Unilateral ischemia; after reduction in renal mass by UNx of the intact kidney and exposure to elevated dietary salt at day 33</td>
<td>Day 63</td>
<td>Renal damage with dilated tubular structures and interstitial infiltration, hypertension</td>
<td>75</td>
</tr>
<tr>
<td>Male Sprague–Dawley rats</td>
<td>Bilateral ischemia (40 min, 37°C)</td>
<td>Days 7 and 33–37</td>
<td>Fibrosis, inflammation, capillary loss, oxidative stress</td>
<td>18,32</td>
</tr>
<tr>
<td>Male large white pigs</td>
<td>Bilateral warm renal ischemia (90 min) or left unilateral warm renal ischemia (90 min) followed by a right nephrectomy</td>
<td>Month 3</td>
<td>Fibrosis</td>
<td>27</td>
</tr>
<tr>
<td>Male large white pigs (31–38 kg)</td>
<td>Left warm renal ischemia (60 min) followed by a right nephrectomy</td>
<td>Month 3</td>
<td>Fibrosis</td>
<td>28</td>
</tr>
<tr>
<td>Male large white pigs (31–38 kg)</td>
<td>Left warm renal ischemia (45, 60, or 90 min) followed by a right nephrectomy</td>
<td>Week 16</td>
<td>Fibrosis</td>
<td>29</td>
</tr>
<tr>
<td>Model: DTR renal epithelial cellmice</td>
<td>Three injections of DT (0.15 μg/kg) at weekly intervals</td>
<td>Day 35</td>
<td>Tubular atrophy, interstitial fibrosis</td>
<td>76</td>
</tr>
<tr>
<td>Model: Reversible unilateral ureteral obstruction</td>
<td>Right ureter was clamped followed by changing the position of the clip every 2 d during the obstruction period (≥3 d); function of the contralateral unmanipulated kidney was removed 7 d after RUOR by left UUO</td>
<td>Day 180</td>
<td>Increases in BUN, fibrosis</td>
<td>77</td>
</tr>
<tr>
<td>Male FVB/N mice (10–12 wk old)</td>
<td>Left UUO for 10 d</td>
<td>Day 21</td>
<td>Dilated proximal tubules and increased collagen deposition in tubulointerstitial areas</td>
<td>78</td>
</tr>
<tr>
<td>Model: Folic acid</td>
<td>ip injection of 250 mg/kg FA dissolved in 0.3 mm sodium bicarbonate</td>
<td>Day 14</td>
<td>Inflammatory cell infiltration, interstitial fibrosis</td>
<td>79</td>
</tr>
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DTR, diphtheria toxin receptor; IRI, ischemia reperfusion injury; UNx, unilateral nephrectomy; DT, diptheria toxin; RUOR, reversible unilateral ureteral obstruction; UUO, unilateral ureteral obstruction; FA, folic acid.
progression. There are several reports showing fibrosis in a pig model of renal I/R injury,27–29 which may represent an important advance in translating potential therapies to larger animals, including humans. Nephrotoxic models and ureteral obstruction models have also been described, again with fibrosis representing a primary end point, but we are not aware of sepsis models in which fibrosis has been evaluated.

Understanding the timing of specific progression and maladaptive repair events in human and animal models of AKI might provide the rationale for targeted treatments at specific points in the course of AKI. For example, capillary loss and myofibroblast activation may occur very early in AKI,17,18 whereas sustained and later interventions.14,23,24 To date, brotic signals derived from maladaptive tubular repair may be suited to both early and later interventions.14,23,24 To date, preclinical studies geared toward recovery from AKI have rarely examined effects on long–term function and progression.

There is a paucity of data in different models to address whether specific insults result in unique maladaptive repair responses affecting progression after AKI. However, because progression after AKI resembles common features of other CKD models,4,5,14 there is reason to believe that targeting established pathways of progression in CKD (e.g., antifibrotic treatments, inhibition of angiotensin II, or hypoxia) may be beneficial in the post-AKI setting.

An important consideration for studies seeking to understand the relative contribution of factors linking AKI to CKD is the degree to which early interventions inhibit the manifestation of the initial injury, thus making it difficult to separate out effects on protection from AKI versus protection against consequences of the initial injury. To address such concerns, whenever possible, experiments should use experimental designs in which treatments commence after the establishment of renal injury (e.g., arginine30). When such maneuvers are not possible (for example, in transgenic animals), effects of specific genes on progression should be conducted after efforts to normalize the acute effects of injury by titrating the injury to equivalent levels using functional biomarkers, such as loss of GFR, creatinine, or KIM-1. In this case, it will be very important to confirm equivalence.

**Question 3. What Are the Relevant Biochemical Pathways Related to Progression That Might Lend Themselves to Therapies?**

Consensus statement: Hypoxia, oxidative stress, epigenetic changes, cell cycle arrest, DNA damage response, and mitochondrial dysfunction represent biochemical pathways with potential for targeting progression of AKI to CKD.

As described above, capillary rarefaction (with resulting hypoxia)5,13 and oxidative stress31,32 may play a major role in both development of AKI and subsequent progression of AKI to CKD. Cells are endowed with powerful defensive mechanisms against hypoxia and oxidative stress (i.e., hypoxia-inducible factor [HIF] and Nrf2), and these may be appropriate therapeutic targets. HIF activation before induction of AKI ameliorates the degree of kidney injury.33 Pharmacologic HIF activation also prevented the development of fibrosis after I/R in mice, an effect that may result from improved tissue repair and suppression of inflammation.34 The antifibrotic effect is not observed if HIF activation occurs after induction of AKI, which may actually exacerbate tissue injury if chronic hypoxia is already present.35

These observations emphasize that there is a narrow therapeutic window of HIF activation (i.e., appropriate timing, duration, and degree of activation). Similarly, exogenous vascular endothelial growth factor administered to preserve renal capillaries also has a therapeutic window only in the early postinjury period, whereas it fails to protect when administered several weeks after injury.36

Pharmacologic Nrf2 activation and subsequent upregulation of antioxidative genes ameliorated experimental bilateral ischemic AKI in mice.37 Pharmacologic Nrf2 activation also improved arsicholic acid–induced AKI in mice.38 Because persistent oxidant stress is a feature of AKI models leading to fibrosis, pharmacologic Nrf2 activation is theoretically a promising approach to attenuate the AKI to CKD transition.

Other biochemical pathways activated as a result of maladaptive repair also represent potential therapeutic targets. For example, prolonged mitochondrial dysfunction induced by AKI may promote progression to fibrosis. Development of fibrosis in the folic acid–induced AKI model was associated with suppression of mitochondrial biogenesis.39 Moreover, epigenetic alterations can be activated after kidney injury, including histone modifications, DNA methylation, and chromosomal conformational changes that regulate gene expression. There have been studies showing that histone deacetylase inhibitors accelerate recovery and decrease postinjury fibrosis after I/R40 and arsicholic acid nephrotoxicity,41 suggesting that epigenetic changes may influence the transition of AKI to CKD.

Maladaptive cellular repair responses may result in progression of fibrosis. As described above, cell cycle arrest of proximal tubules at the G2/M phase of the cell cycle activates c-jun NH(2)–terminal kinase signaling and promotes subsequent development of fibrosis.44 In response to DNA damage, cells activate a network of signaling pathways known as the DNA damage response (DDR). Activation of DDR sensor protein kinases is followed by activation of the executor kinases and subsequent phosphorylation of proteins to induce cell cycle arrest or eventual cell death. DDR can be induced by oxidative stress–related DNA damage in the kidney of a model of ischemic AKI.42 Because of its effects on G2/M arrest, DDR has been implicated in fibrosis of the kidney.44 In contrast, transient early G0/G1 arrest in renal epithelial cells protects these cells from DNA damage and apoptosis in a model of AKI,43 suggesting that specific cell cycle targeting may be beneficial.

It is of interest that several biochemical pathways hypothesized to mediate protection have been identified by strategies, such as preconditioning, which
may be active concurrent with adaptive or maladaptive repair processes. Intuitively, some of these pathways may be protective against acute injury, such as HIF, Nrf2, heat shock proteins, and antioxidants, whereas their effects on chronic injury have not been specifically addressed. The potential maladaptive effects of preconditioning were illustrated in a classic study by Nath et al., in which repeated glycerol treatment protected rats acutely from subsequent glycerol injections, while they developed more significant interstitial fibrosis. Thus, preconditioning responses may be acutely beneficial but chronically deleterious. It is unclear if the same pathways are involved in both acute protection and chronic progression. In this context, we suggest that future studies of this nature consider both acute and chronic effects of these strategies on renal function.

**Question 4. Can Progression to CKD Be Predicted after AKI and Risk Factors Are Identified?**

Consensus statement: Progression from AKI depends on the balance of adaptive and maladaptive repair, and an understanding of these events is key to predicting the degree of progression.

It is already known that the severity, duration, and frequency of episodes of AKI as well as age, preexisting CKD, and other comorbidities are associated with a greater risk for progression. However, it is often difficult to recognize clinically and biochemically whether a step change in renal function in a patient with known CKD represents progression of the underlying disease or is the result of a new insult. To date, available animal models of AKI superimposed on CKD are limited, and no specific biomarkers have been identified to distinguish progression after AKI from progression of underlying CKD or how they might interact.

Hence, evaluation of biomarkers indicative of adaptive and maladaptive repair represents the key to defining predictability. One predictive biomarker is serum creatinine concentration; the severity of AKI as determined by the change in serum creatinine during the AKI episode has been linked to subsequent development of ESRD. In addition, the number of documented AKI episodes in a population of patients with diabetes was found to be associated with increased risk for developing stage 4 CKD.

There are other biomarkers that may also be predictive for CKD. For example, KIM-1 has been shown to be a predictor of both AKI and progression of CKD in patients with type 1 diabetes. Increases in serum levels of FGF23 and parathyroid hormone or decreased levels of Klotho occur in response to increased severity of CKD. Biomarkers, such as urinary albumin, neutrophil gelatinase-associated lipocalin, KIM-1, IL-18, L-FABP MCP-1, nephrin, podocalyxin, and podocin, are markers of tubular or glomerular damage. Other biomarkers, such as C-reactive protein and TNF receptor 2, which are general biomarkers of inflammation or endothelial dysfunction, may reflect systemic phenomena relevant to CKD progression, but their predictive value after AKI is unknown.

Additional biomarker approaches may also be considered. Epigenetic factors have been implicated in the development of fibrosis in the rodent. In the Chronic Renal Insufficiency Cohort Study, which was established to follow a diverse group of patients with chronic renal insufficiency with intensive screening and follow-up for the purpose of identifying high-risk groups, patients characterized as rapid progressors had different DNA methylation profiles on a number of genes that have been implicated in inflammation or fibrosis, including TGF-β.

The hallmark of progression is the development of fibrosis, but at this time, there is no Food and Drug Administration–qualified biomarker useful in the longitudinal monitoring of intrarenal fibrosis. Efforts, such as the National Institutes of Health (NIH) - National Institute of Diabetes and Digestive and Kidney Diseases–funded CKD Biomarker Consortium, seek to identify biomarkers that can predict which patients with CKD will progress more rapidly, and biomarkers that can be used to monitor progression. Markers, such as urinary connective tissue growth factor, may reflect the degree of intrarenal fibrosis along with other markers of extracellular matrix metabolism, such as matrix metalloproteinases, tissue inhibitors of metalloproteinases, and type 4 collagen, and these could represent predictive biomarkers.

Imaging applications to noninvasively assess the degree of interstitial fibrosis or other functional aspects of CKD may be on the horizon. For example, renal hypoxia has been measured in patients after AKI and patients with progressive CKD using blood oxygen level–dependent magnetic resonance imaging (MRI). Fibrosis–specific contrast agents designed to target collagen in MRI studies and Cu–labeled collagen–specific peptides used in PET imaging have been reported to detect renal or cardiac fibrosis models. Elastography techniques have been developed using MRI or ultrasound imaging that measure tissue sample stiffness; these techniques have been applied in preclinical models of kidney fibrosis. These novel approaches to evaluate renal fibrosis noninvasively have garnered significant attention from the NIH, because they would represent a powerful diagnostic advance particular in the identification of those susceptible to CKD after AKI.

It is likely that a quantitative evaluation of more than one biomarker will be necessary to distinguish between an acute exacerbation of an underlying disease and a new process superimposed on underlying CKD. Combining injury markers with functional markers, such as changes in serum creatinine, cystatin C, or β-trace protein, may provide a predictive insight as to the long-term consequences of AKI. For example, an increase in injury biomarkers together with an elevation of serum creatinine may portend a worse outcome than an elevation in either one alone.

**Question 5. What Are the Best Treatment Strategies for Targeting Progression?**

Consensus statement: At this time, there are no therapeutic interventions targeting progression. Emerging biomarkers...
may help in identifying specific targets and time points for intervention. Focused attention on modifiable risk factors for progression (e.g., hypertension) is key to preventing progression.

Currently, there are no therapeutic interventions targeting progression after AKI. There are unanswered questions that present barriers to progress. We often do not know when the AKI insult occurred, its nature, or at which point we can or should intervene. When have reparative processes failed, leading to sustained cell injury, cell loss, and eventual fibrosis? Is fibrosis per se the process that we should target, or should we target underlying mechanisms (e.g., tissue perfusion and/or hypoxia)? Efforts to maintain the latter with, for example, vascular endothelial growth factor or increasing HIF expression have shown benefit in experimental models but only when given before or soon after any injury (a situation that will be hard to replicate in human AKI). Additionally, we are constrained by a lack of histopathology, because biopsies in patients with AKI are uncommon. We, therefore, lack a good understanding of structural-function correlations in AKI. Finally, we need better animal models that mimic all aspects of human AKI, especially because many humans have underlying comorbidities that interact with the acute insult to dictate risk for progression.

Although these problems seem formidable, there is hope on the horizon. Newer biomarkers combined with functional markers hold promise to identify the phase, nature, and severity of injury. Although currently, there are only a few studies that have assessed the prognostic value of novel biomarkers, except for perhaps, recently, blood KIM-1 levels. Perhaps, recently, blood KIM-1 levels value of novel biomarkers, except for studies that have assessed the prognostic importance of hemodynamic changes early on, including fluid balance and BP, as well as any markers of a maladaptive systemic inflammatory response that can and should be suppressed. Risk scores identifying patients likely to progress are being proposed and if validated, would provide an opportunity for earlier intervention.

It is unknown at this point whether a patient with CKD and a history of AKI should be managed any differently than a patient with CKD without such a history given that both may have another underlying cause for CKD and that we have so few treatment options. More information is required from detailed clinical observation, carefully conducted long-term trials, and/or better animal models that can provide a greater understanding of the pathophysiology of progression of CKD post-AKI.

ACKNOWLEDGMENTS

A complete list of participants is provided in Supplemental Appendix.

DISCLOSURES


REFERENCES

SPECIAL ARTICLE


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Progression after AKI

695


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