Acute Kidney Injury to Chronic Kidney Disease Transition

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850,000,000+
People world wide have kidney diseases

843,000,000
CKD 1-5
10.4% men and 11.8% women

13,300,000
Acute Kidney Injury

7,000,000
ESRD

3,900,000
Treated with RRT

40 M

AKI, CKD and ESRD

84 YOM with stage IV CKD, DM-2, CHF, COPD admitted with hypoglycemia, SBO with nausea and vomiting. Pt was volume depleted with SCr of 5.5.

From Bruce Molitoris
Systematic review of chronic kidney disease and ESRD associated with acute kidney injury

**CKD**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Weight (%)</th>
<th>Hazard ratio IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss <em>et al.</em> (13)</td>
<td>10.0</td>
<td>32.79 (4.30–249.77)</td>
</tr>
<tr>
<td>Amdur <em>et al.</em> (22)</td>
<td>15.5</td>
<td>6.64 (5.05–8.74)</td>
</tr>
<tr>
<td>Lo <em>et al.</em> (11)</td>
<td>15.5</td>
<td>28.08 (21.01–37.53)</td>
</tr>
<tr>
<td>James <em>et al.</em> (16)</td>
<td>15.6</td>
<td>29.99 (24.32–36.99)</td>
</tr>
<tr>
<td>James <em>et al.</em> (15,23)</td>
<td>15.5</td>
<td>1.60 (1.20–2.14)</td>
</tr>
<tr>
<td>Ando <em>et al.</em> (19)</td>
<td>12.4</td>
<td>9.91 (2.48–39.63)</td>
</tr>
<tr>
<td>Ishani <em>et al.</em> (21)</td>
<td>15.6</td>
<td>2.33 (1.83–2.96)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0</td>
<td>8.82 (3.05–25.48)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.87$; $\chi^2 = 446.89$, d.f. = 6 ($P < 0.00001$); $I^2 = 99\%$. Test for overall effect: $Z = 4.02$ ($P < 0.0001$)

**ESRD**

<table>
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<th>Study or subgroup</th>
<th>Weight (%)</th>
<th>Hazard ratio IV, random, 95% CI</th>
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<td>Newsome <em>et al.</em> (14)</td>
<td>15.0</td>
<td>3.26 (2.87–3.70)</td>
</tr>
<tr>
<td>Ishani <em>et al.</em> (20)</td>
<td>14.8</td>
<td>12.99 (10.57–15.96)</td>
</tr>
<tr>
<td>Wald <em>et al.</em> (17)</td>
<td>14.9</td>
<td>3.22 (2.70–3.85)</td>
</tr>
<tr>
<td>Hsu <em>et al.</em> (10)</td>
<td>13.5</td>
<td>1.47 (0.95–2.28)</td>
</tr>
<tr>
<td>James <em>et al.</em> (15,23)</td>
<td>12.5</td>
<td>4.15 (2.32–7.41)</td>
</tr>
<tr>
<td>Lafrance <em>et al.</em> (18)</td>
<td>15.0</td>
<td>2.33 (2.08–2.61)</td>
</tr>
<tr>
<td>Choi <em>et al.</em> (12)</td>
<td>14.4</td>
<td>1.37 (1.02–1.84)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0</td>
<td>3.10 (1.91–5.03)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.40$; $\chi^2 = 252.85$, d.f. = 6 ($P < 0.00001$); $I^2 = 98\%$. Test for overall effect: $Z = 4.58$ ($P < 0.00001$)

Mortality after acute kidney injury

Traditional risk factors, such as chronic hypertension, dyslipidemia contribute LVH in CKD affects 50%–70% of patients during intermediate stages of CKD. 90% of patients by the time they reach dialysis.

CKD increases sensitivity to CV events

Loss of Windkessel Physiology

Arterial Calcification

FGF23 induces left ventricular hypertrophy

Indoxyl sulfate (IS) is produced by intestinal bacteria; degradation product of tryptophan; in liver IS is produced by cytochrome P450–mediated hydroxylation of indole to indoxyl, f/b sulfotransferase-mediated sulfate conjugation. AST-120 an adsorbent reverses effect of IS, in clinic trials (ClinicalTrials.gov).
AKI-CKD
Redifferentiation, recovery vs failed redifferentiation and growth arrest

M.A. Venkatachalam et al. JASN 26:1765-1776, 2015
Failed tubule differentiation and atrophy and fibrosis is restricted to diseased microenvironment.

Extension of fibrosis requires additional insult, continued inflammation, hypoxia or hyperfiltration in remnant nephrons.

Nexus of AKI and CKD/ESRD

Cardiovascular Events

Disease Modifiers
- Severity of AKI
- CKD Stage
- No Episodes
- Duration of AKI
- Proteinuria

Outcomes
- Age
- Racial/ethnic group
- Genetic factors
- Hypertension
- Diabetes
- Metabolic syndrome

Risk Factors

CKD

ESRD

Disability and Diminished QOL

Death
Capillary Dropout In Postischemic Kidney

20 µm Microfil-infused Kidney Sections

Sham  4 weeks  8 weeks

DP Basile et al. AJP Renal 281: F887-F899, 2001
High-Resolution in vivo ex vivo Micro – CT

Ex vivo Microfil Perfusion and Vascular Casting

In vivo Contrast Enhanced

Renal Vasculature following acute kidney injury

Capillary rarefaction increases the diffusion distance for oxygen transport in tissues

Loss of Peritubular Capillaries Leads to Chronic Hypoxia

M Nangaku, JASN 2006;17:17-25
Tubule specific injury can drive fibrosis:

*Transgenic mice overexpressing KIM-1 in proximal tubules leads to progressive fibrosis*

- Tubules and capillaries are simultaneously injured
- Direct tubule damage can be sufficient to induce fibrosis
**Endothelium**

Microvascular endothelial injury and dysfunction during IRI: Endothelial Sphingosine 1 phosphate receptor 1

Ischemia

Endothelial Cell activation, Dysfunction, Injury and/or Detachment

Impaired Vasodilation
Coagulation
Leukocyte Adhesion

Capillary Obstruction and Continued Ischemia

Extension of ARF

Acute Kidney Injury Pathogenesis

Endothelial, Epithelial, Immune Cells and Interstitium

L. Li et al. Kidney Int. 2008 74:1526-37
Chronic Inflammation and Fibrosis: Microenvironment

Origin of myofibroblasts in the kidney

Pericytes: interstitial fibrosis after AKI

- **Pericytes** are contractile cells that wrap around endothelial cells and line capillaries and contact tubules.
  - Communicate with endothelial cells by contact and paracrine signaling.
  - After injury PC-EC detachment occurs from EC: PDGFRβ-mediated migration and transformation of fibroblasts/pericytes → myofibroblasts causing
  - loss of endothelial integrity.
- The microenvironment activates interstitial precursor cells that become myofibroblasts → proliferate and make connective tissue
  - humoral factors from regenerating tubules
  - Inflammatory cells, including monocytes, lymphocytes, and dendritic cells
- By lineage analysis are derived from FoxD1-expressing embryonic progenitors.

Endothelial Cells and Pericytes in Fibrosis

Expansion of Labeled Interstitial Pericytes During Fibrosis

Pericytes detach from endothelial cells following IRI
Capillary rarefaction after Gli1+ pericyte ablation

Importance of PC-EC contact to maintain normal function

Phase-dependent macrophage phenotypic change during the progress of kidney diseases

L. Li et al. Kidney Int. 2008 74:1526-37
Microenvironment determines phenotypic switch of macrophages during the course of AKI and CKD

Qi Cao et al. Physiology 2015;30:183-194
Microenvironmental Factors controlling Macrophage Phenotype

F4/80+
Proinflammatory
Wound Healing

iNOS
Arg-1

Mitochondria and Fibrosis

M. Zhan...Z. Dong, Kidney International (2013) 83, 568–581;
Proximal Tubule Deficient of Drp1 is protected from Fibrosis

\[ i\text{Drp}1^{WT} \quad i\text{Drp}1^{PTKO} \]

Unilateral IRI
Tamoxifen
analysis

Day: 0 3 4 5 6 7 13 14

iSLC34a1CreER\(^T2\) mouse gift of B. Humphreys

HM Perry and MD Okusa unpublished observations 2017
Cardiolipin-protective compound – SS31 restores mitochondrial bioenergetics

- CL – phospholipid expressed on the inner mitochondrial membrane; important structural role in cristae formation and the organization of the respiratory complexes into supercomplexes for optimal OX PHOS.
- The interaction between CL and cytochrome c determines whether cytochrome c acts as an electron carrier or peroxidase.
- SS-31 is a member of the Szeto-Schiller (SS) peptides targets the inner mitochondrial membrane. SS-31 carries 3+ charge and binds to anionic phospholipid CL.
- SS-31 prevents CL from converting cytochrome c into a peroxidase - protecting its electron carrying function.
- SS-31 protects the structure of mitochondrial cristae and promotes oxidative phosphorylation.
SS-31 Preserves Mitochondria and arrests CKD Progression

HH Szeto et al. JASN November 23, 2016
Molecular Mechanisms of Fibrosis

Cell Cycle and Epigenetic Modification


Rasal 1

↓

RAS inactivation

↓

Cell Proliferation

Hypermethylation

Rasal 1

↓

RAS activation

↑

Cell Proliferation
Tgf-β induces proximal tubule partial EMT and cell cycle arrest

- After injury, TGF-β promotes Snail1 and Twist expression, which activates EMT program → incomplete EMT.
- Partial EMT → cell-cycle arrest → to tissue dysfunction.
- Partial EMT drives proliferation of myofibroblasts by the secretion of growth factors, including TGF-β.
- Partial EMT fuels chronic inflammation.

Metabolic alterations in AKI-CKD

*Metabolic switch in energy metabolism*

- AKI and failed regeneration, PT undergoing atrophy-mitochondrial alterations- persistent glycolytic activity
  - ↑ glycolysis, ↑ glycolytic enzyme expression
- Humans and mouse models with tubulointerstitial fibrosis:
  - lower expression of key enzymes and regulators of fatty acid oxidation
  - higher intracellular lipid deposition compared to controls.
- Inhibition of FAO in tubule epithelial cells caused ATP depletion, cell death, dedifferentiation and intracellular lipid deposition, seen in fibrosis.
  - Restoration of fatty acid metabolism by genetic or pharmacological methods protected mice from tubulointerstitial fibrosis.

Acute Kidney Injury and Fibrosis

Endothelium

Fibroblast/Pericyte

Epithelium

Myofibroblast

FAO
Ox Phos
Glycolysis
Mitochondria Structure
Mitochondria Function

Capillary Rarefaction

Fibrosis