The Link Between Acute and Chronic Kidney Disease

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Conventional Dogma

• Conventional dogma was that if a patient survived and recovered from AKI, he was unlikely to have long-term sequelae.
• Older studies did not have comparison groups of patients with similar characteristics who did not develop AKI.
• Comparison of outcomes of patients with and without AKI could not be made.
Minnesota Study

• 432 patients dialyzed at University of Minnesota for ATN.
• 31% (135 survived).
• Serum creatinine fell for 1 month and then stabilized.
• No control group.
• “The majority of patients have no clinical problem of renal dysfunction if they survive their basic disease leading to ATN”

Danish Study of Long Term Outcomes of AKI

419 patients with dialysis-requiring AKI. Match population not discussed.
“In conclusion...outcome seems almost solely dependent on the severity and progression of the underlying disease process.”

Recent Study Suggested that AKI not Associated with CKD

- 413 patients with ATN and rise in SCr of at least 2 mg/dl at hospitals in Madrid. 187 survived and were followed between 6 months and 22 years.

- “Although the late mortality rate is high and related with the original disease, renal function is adequate in most patients.”

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal renal function (n=46)</th>
<th>Mild renal insufficiency (n=9)</th>
<th>Moderate renal insufficiency (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.1±0.2</td>
<td>1.7±0.1</td>
<td>3.3±1.5</td>
</tr>
</tbody>
</table>

Liaño et al Kidney Int. 2007
Recent Studies Show Strong Correlation Between AKI and CKD

• Prior to 2009, it was generally considered that patients who recovered from AKI had no long term sequelae beyond that caused by the underlying disease.
• Beginning about 2009, multiple studies showed adverse outcomes in patients with AKI
  – Development of CKD
  – ESRD
  – Mortality
  – Cardiovascular death
Time from diagnosis to combined end point (the earliest of CKD-4, chronic dialysis, or death)

Comparison of 5404 patients in the VA with a diagnosis of ATN or ARF to control patients with a diagnosis of AMI or pneumonia.

Amdur et al. Kidney Int. 2009
AKI Increases the Risk of Development of CKD Stage 4 or 5

556,090 adult in Kaiser Permanente system in N California
Baseline eGFR ≥ 45
703 required dialysis
295 died
65 did not regain renal function

343 Dialysis requiring AKI
28-fold increase in risk

No AKI

Lo et al. Kidney Int. 2009
Risk of ESRD Increases with AKI

Random sample of Medicare beneficiary claims. AKI and CKD by claims data. Linked to USRDS database for ESRD outcome.

Small Increases in SCr Increase risk of ESRD

Patients with diagnosis codes for acute myocardial infarction. Serum creatinine values obtained from record by trained abstractors. ESRD and mortality obtained from USRDS and Medicare Enrollment Database.

Adjusted for age, sex, race, history of stroke, hypertension, diabetes mellitus, previous MI, smoking status, admission eGFR and anemia.
Small Increases in SCr Increase risk of Mortality

Long-term Renal Function Associated with Severity of AKI

Chawla et al. Kidney Int. 2011

VA patients identified by diagnosis code. Serum creatinine obtained from EMR.
Risk of Stage 4 CKD Increases with Each Episode of AKI
VA patients with diabetes

Thakar et al. CJASN 2011;6:2567-2572

AKI defined by AKIN SCr criteria.
### 3-5 year outcomes after AKI in children

<table>
<thead>
<tr>
<th></th>
<th>CRF (CCl&lt;90 ml/min)</th>
<th>Normal (90&lt;CCl &gt;150 ml/min)</th>
<th>Hyperfiltration (CCl&gt;150 ml/mi)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal urine albumin/creatinine</td>
<td>2</td>
<td>14</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Microalbuminuria urine Alb/Cr&gt;30</td>
<td>2</td>
<td>2</td>
<td>4*</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>16</td>
<td>9</td>
<td>29</td>
</tr>
</tbody>
</table>

Selected based on diagnosis of ARF on discharge summary
126 patients eligible for long term follow up. Unable to locate 69. 28 refused or did not show up for follow-up. 29 patients assessed.
13 out of 29 had some abnormality in renal function at follow-up

Askenzi et al., Kidney Int. 2006
Meta-analysis: Risk of CKD after AKI

<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 et al. (13)</td>
<td>10.0</td>
<td>32.79 (4.30–249.77)</td>
</tr>
<tr>
<td>Amdur et al. (22)</td>
<td>15.5</td>
<td>6.64 (5.05–8.74)</td>
</tr>
<tr>
<td>Lo et al. (11)</td>
<td>15.5</td>
<td>28.08 (21.01–37.53)</td>
</tr>
<tr>
<td>James et al. (16)</td>
<td>15.6</td>
<td>29.99 (24.32–36.99)</td>
</tr>
<tr>
<td>James et al. (15,23)</td>
<td>15.5</td>
<td>1.60 (1.20–2.14)</td>
</tr>
<tr>
<td>Ando et al. (19)</td>
<td>12.4</td>
<td>9.91 (2.48–39.63)</td>
</tr>
<tr>
<td>Ishani et al. (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: $\chi^2 = 1.87$; $\chi^2 = 446.89$, d.f. = 6 ($P < 0.00001$); $I^2 = 99\%$. Test for overall effect: $Z = 4.02$ ($P < 0.0001$)

Pooled hazard ratio for CKD risk 8.8 (95% CI 3.1-25.5)

Coca et al. Kidney Int. 2012
Meta-analysis: Risk of ESRD after AKI

Pooled hazard ratio for ESRD 3.1 (95% CI 1.9-5.0)

Pooled hazard ratio for Death 2.0 (95% CI 1.3-3.1)

Coca et al. Kidney Int. 2012
AKI and Risk of CKD

• Previous studies did not include comparator groups to determine relative risk of patients with AKI.
• Recent retrospective studies strongly suggest that AKI increases the risk for CKD, ESRD and mortality.
• There are no large prospective studies to confirm the association. Causation has not been proven but there is a suggestion that it may be causative.
Clinical Implications of AKI-CKD link

• KDIGO 2012 AKI Guidelines recommend 3 month follow up after AKI.

• 2.3.4: Evaluate patients 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD. *(Not Graded)*
  
  – Assessment of eGFR and albuminuria at 3 months
  
  – If they do not have CKD at 3 months. They should be considered at increased at risk for CKD.
Evidence that AKI Causes CKD

• Increased severity of AKI associated with development of CKD.
• Multiple episodes of AKI increase risk for CKD.
• CKD risk increased in children with AKI (with fewer co-morbidities).
• AKI is independently associated with adverse outcomes which are also associated with CKD.
Mechanistic Links Between AKI and CKD

- Nephron loss in AKI
- Promotion of fibrosis though inflammatory pathways
- Endothelial injury and loss of capillaries
- Cell cycle arrest
Potential Mechanisms of AKI to CKD Transitions

Nephron Loss After AKI

Venkatachalam et al. Am J. Physiol-Renal. 2010
Cycle of Injury Leading to Fibrosis and Hypoxia

Epithelial injury produces paracrine factors which potentiate injury through enhanced inflammation, fibroblast activity, reduced capillary blood flow and hypoxia.

Venkatachalam et al. Am J. Physiol-Renal. 2010
Inflammatory Cells Migrate into Interstitium

Devarajan, J Am Soc Neph. 2006
Role of Macrophages in Fibrosis

Renal microvascular structure is altered after I/R injury

P21 and Cell Cycle after AKI

(a) Western blots showing expression of P21 in control, ischemia, obstruction, and cisplatin-treated samples over time.

(b) Immunohistochemical staining of kidney tissue showing P21 expression.

(c) Higher magnification of P21-positive cells in kidney tissue.

(d) Graph showing BUN levels over time in p21(-/-) and p21(+/-) mice, with statistical significance indicated.

(e) Survival curve showing lower survival rates in p21(-/-) compared to p21(+/-) mice, with statistical significance indicated.

Price et al. Kidney Int. 2009
Models of AKI Develop Different Amounts of Fibrosis and Different Degrees of Cell Cycle Arrest

Yang et al. Nat Med. 2010
Decreasing Cell Cycle Arrest Decreases Production of Fibrogenic Mediators

Fibrogenic mediators increase is correlated with cell cycle arrest

Yang et al. Nat Med. 2010
Complex and Interrelated Mechanisms of Acute to Chronic Transitions

Summary

• Prior to the late 2000’s AKI was not thought to cause adverse outcomes if the patient recovered from the acute episode.

• Recent retrospective data demonstrate an association between AKI and adverse outcomes although there are not yet prospective trials.

• Current (KDIGO) guidelines recommend follow-up of patients after an episode of AKI.

• Animal models suggest multiple mechanisms may be responsible for chronic kidney disease after AKI.