11th Annual National Summit on Health Disparities

Racial Disparities in CKD: Role of NIH in Fostering Innovative Research

Michael F Flessner, MD, PhD
Program Director, Inflammatory Renal Disease
Division of Kidney, Urologic, and Hematologic Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

April 28, 2014
“Science in pursuit of **fundamental knowledge** about the nature and behavior of living systems...”

“...and the **application of that knowledge** to extend healthy life and reduce the burdens of illness and disability.”
NIH: 27 Institutes and Centers
The NIDDK Research Mission

To support and conduct research to combat diabetes and other endocrine and metabolic diseases, liver and other digestive diseases, nutritional disorders, obesity, and kidney, urologic and hematologic diseases.
Outline

• Defining the Problem: Observational Studies
  – USRDS
  – Jackson Heart Study, HSOL
  – CRIC - CKID

• Innovative Solutions
  – NKDEP
  – Biomarkers Consortium
  – CKD Pilot Trials
  – TIME Trial
Chronic Kidney Disease

Growing % of Population

Consequences

Mortality rates

37% HIGHER

54 74

No CKD All CKD

Hospitalization rates

38% HIGHER

307 423

No CKD All CKD

Costs

Overall, patients with CKD account for 18% of total Medicare expenditures

CKD patients with congestive heart failure account for 39% of Medicare CHF expenditures

Cost to Medicare for CKD: $45 B in 2011

CKD population growing
Driven by obesity, diabetes, and aging population

Die from cardiovascular disease: stroke, heart attack, and congestive heart failure

USRDS ADR, 2013
Adjusted odds ratio of a CKD diagnosis code in Medicare patients, by age, gender, & race, 2011

Figure 2.6 (Volume 1)

Medicare patients age 65 & older, alive & eligible for all of 2011. CKD claims as well as other diseases identified in 2011.

USRDS ADR, 2013
Unadjusted rates of first AKI within the cohort year among Medicare patients age 66 & older, by race

Figure 6.4 (Volume 1)
End Stage Renal Disease (ESRD)
Includes Dialysis and Transplantation

Number of Patients

- Prevalent dialysis (2011: 430,273)
- Prevalent transplant (185,626)
- Incident ESRD (115,643)

Dialysis population growing 5%/yr
Number of new patients stabilized, except in African Americans

5-year Survival

Survival worst in first 6 months

Costs

1.4% of Medicare patients have ESRD
They account for 7.2% of Medicare spending

Total cost of ESRD patient care: $49 B in 2011

USRDS ADR, 2013
Adjusted incidence rates of new ESRD patients, per million population. Adjusted for age/gender/race/ethnicity

1980
1 in 11,000

2011
1 in 2,800

USRDS ADR, 2013
Adjusted incident rates of ESRD due to hypertension, by age, race, & ethnicity

Figure 1.9 (Volume 2)
Prevalent counts & adjusted rates of ESRD, by Hispanic ethnicity

December 31 point prevalent ESRD patients.
Adj: age/gender; ref: 2010 ESRD patients.

USRDS ADR, 2013
## Need to Transform Medical Research in the 21st Century

<table>
<thead>
<tr>
<th>20th Century</th>
<th>21st Century</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat disease when symptoms appear and normal function is lost</td>
<td>Intervene before symptoms appear and preserve normal function for as long as possible</td>
</tr>
<tr>
<td>Did not understand the molecular and cellular events that lead to disease</td>
<td>Understand preclinical molecular events and detect patients at risk</td>
</tr>
<tr>
<td>Expensive in financial and disability costs</td>
<td>Orders of magnitude more effective</td>
</tr>
</tbody>
</table>
Outline

• Defining the Problem: Observational Studies
  – USRDS
  – Jackson Heart Study, HSOL
  – CRIC - CKID

• Innovative Solutions
  – NKDEP
  – Biomarkers Consortium
  – CKD Pilot Trials
  – TIME Trial
Prevalence of CKD in JHS

men = solid bars; women = open bars
Low Awareness is more often the problem of the practitioner.
Prevalence of CKD in Hispanics/Latinos and non-Hispanic Whites and Blacks by Gender

Women

- eGFR < 60 ml/min/1.73 m²
- ACR ≥ 30 mg/g
- CKD

Men

- eGFR < 60 ml/min/1.73 m²
- ACR ≥ 30 mg/g
- CKD

Weighted Prevalence, %

Courtesy J Lash, HSOL
• Defining the Problem: Observational Studies
  – USRDS
  – Jackson Heart Study, HSOL
  – CRIC – Chronic Renal Insufficiency Cohort
  – CKID – CKD in Children Cohort

• Innovative Solutions
  – NKDEP
  – Biomarkers Consortium
  – CKD Pilot Trials
  – TIME Trial
NIDDK’s CRIC Study

• Landmark study of causes and consequences of chronic kidney disease (CKD)
  – 5500 Americans enrolled at 13 medical centers
  – Followed up to 10 years
# Recruitment in CRIC

3,939 participants between 5/03 and 8/08

<table>
<thead>
<tr>
<th>Selected Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic</td>
<td>12.6%</td>
</tr>
<tr>
<td>African American</td>
<td>42.1%</td>
</tr>
<tr>
<td>Diabetic</td>
<td>48.4%</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>21-44 yrs</td>
<td>13.7%</td>
</tr>
<tr>
<td>45-64 yrs</td>
<td>57.4%</td>
</tr>
<tr>
<td>65-74 yrs</td>
<td>28.9%</td>
</tr>
</tbody>
</table>
The Hispanic Chronic Renal Insufficiency Cohort (CRIC) Study is an prospective observational study of individuals with mild to moderate CKD, sponsored by the Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

The overall aims are:

- To determine predictors of progression of kidney disease and subclinical CVD in Hispanics with CKD.
- To compare rates of progression of kidney disease and subclinical CVD in Hispanics with CKD to those seen in non-Hispanics Whites and Blacks.
Multiple Dimensions of CRIC

**Study Populations**
- Advanced CKD
- Hispanics
- Diabetics
- Racial groups

**Exposures**
- eGFR
- BP
- Inflammation
- Mineral Metabolism
- Medications

**Outcomes**
- ESRD
- CVD
- Functional Status
RATES OF CKD PROGRESSION

![Bar chart showing rates of CKD progression by ethnicity: NH White, NH Black, Hispanic.](chart.png)

*Fischer et al. American Society of Nephrology Kidney Week Presentation 2012*

* p<0.05
## CKiD vs CRIC cohorts - baseline

<table>
<thead>
<tr>
<th></th>
<th>CKiD (medians)</th>
<th>CRIC (means)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>11</td>
<td>58.2 ±11</td>
</tr>
<tr>
<td><strong>GFR, ml/min/1.73m2</strong></td>
<td>43</td>
<td>43.4±13.5</td>
</tr>
<tr>
<td><strong>Prevalence of diabetes</strong></td>
<td>0</td>
<td>47%</td>
</tr>
<tr>
<td><strong>Tobacco use</strong></td>
<td>?</td>
<td>14% current; 56% &gt;100 cig</td>
</tr>
<tr>
<td><strong>History of HTN</strong></td>
<td>47%</td>
<td>86%</td>
</tr>
<tr>
<td><strong>ACEi/ARB use</strong></td>
<td>59%</td>
<td>70%</td>
</tr>
<tr>
<td><strong>History of MI/CHF/PAS</strong></td>
<td>0</td>
<td>22%/10%/7%</td>
</tr>
<tr>
<td><strong>Prevalence of obesity</strong></td>
<td>24% (BMI &gt;90%tile)</td>
<td>55% (BMI &gt;30)</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
<td>12.5</td>
<td>12.7</td>
</tr>
<tr>
<td><strong>Total cholesterol</strong></td>
<td>175</td>
<td>183</td>
</tr>
<tr>
<td><strong>HDL cholesterol</strong></td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>116</td>
<td>154</td>
</tr>
<tr>
<td><strong>LVH at baseline</strong></td>
<td>17%</td>
<td>54%</td>
</tr>
</tbody>
</table>
• Defining the Problem: Observational Studies
  – USRDS
  – Jackson Heart Study, HSOL
  – CRIC - CKID

• Innovative Solutions
  – NKDEP = National Kidney Disease Education Project
  – Biomarkers Consortium
  – CKD Pilot Trials
  – TIME Trial
You have two kidneys, each about the size of your fist.

The keep the body’s chemical balance and help control blood pressure. They filter wastes and excess water out of your blood to make urine.

Chronic kidney disease (CKD) means that your kidneys are damaged and can’t filter blood like they should.

CKD is often a “progressive” disease, which means it can get worse over time.
Key Questions
What is my GFR?
What is my urine albumin result?
What is my blood pressure?
What is my blood glucose (for people with diabetes)?

Other Important Questions
What happens if I have kidney disease?
What should I do to keep my kidneys healthy?
Do I need to be taking different medicines?
Should I be more physically active?
What kind of physical activity can I do?
What can I eat?
Do I need to talk with a dietitian to get help with meal planning?
Should I be taking ACE inhibitors or ARBs for my kidneys?
How often should I get my kidneys checked?
Outline

• Defining the Problem: Observational Studies
  – USRDS
  – Jackson Heart Study, HSOL
  – CRIC - CKID

• Innovative Solutions
  – NKDEP
  – Biomarkers Consortium
  – CKD Pilot Trials
  – CURE-GN
Increased Kidney Disease Risk Among African Americans Mostly Explained by ApoL1 Gene Mutation

**ESRD rates by race**

![Graph showing ESRD rates by race](image)

**Lifetime risk for ESRD**
- **Whites** ~2%
- **Blacks** ~7.5%

**Apolipoprotein L1 (APOL1): kidney risk copies**

<table>
<thead>
<tr>
<th></th>
<th>0 copies</th>
<th>1 copy</th>
<th>2 copies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>African Americans</strong></td>
<td>42%</td>
<td>46%</td>
<td>12%</td>
</tr>
<tr>
<td>FSGS risk (lifetime)</td>
<td>0.2%</td>
<td>0.3%</td>
<td>4% (25-fold increase)</td>
</tr>
<tr>
<td>Hypertensive kidney disease risk</td>
<td>--</td>
<td>--</td>
<td>~5-10% (5-fold increase)</td>
</tr>
</tbody>
</table>
Our Genes Determine How Fast our CKD Worsens

Novel Biomarkers Strongly Predict Death in CKD

CKD Associated with Important Eye Abnormalities

Pre-retinal hemorrhage

Hypertensive retinopathy

CKD Associated with Stiffening of Blood Vessels

FGF-23
• Innovative Solutions
  – NKDEP
  – Biomarkers Consortium
  – CKD Pilot Trials (Test Generic Drugs)
    • Control phosphorus and FGF-23
    • Give Bicarbonate to decrease acid and inflammation
    • Improve the colonic microbiome (pre-biotic)
  – CURE-GN (Glomerular Diseases)
    • Future Cohort of 2400 with IgA, MCD, MN, FSGS
    • Biomarkers, pathology, genetics, clinical course
    • Drug interventions (industry collaborators)
NIDDK Investments in CKD

**CKD Clinical Trial Network**
- Modify FGF23
- Bicarbonate
- Microbiome
- Allopurinol

**Glomerular Disease Network**

**Testing innovative biomarkers**: FGF23, complement, serum proteomics

**ApoL1**: 10x ↑ risk CKD
**FGF23**: ↑ risk CKD, CVD

**Adolescent Heart disease**

**Craniocerebral Insults**

**USRDS**

**Longitudinal and Clinical Observations (Progression)**

**Epidemiology (Risk Factors)**

**Enhancing Knowledge Improving Outcomes**

**Basic / Translation Research (Regression)**

**Clinical Trials (Intervention)**

**Regular Research Grants**
- Human GUDMAP
- Fibrosis Consortium
Thanks for your attention!
“Extra” slides
NIH Investments in ESRD

Improve survival and quality of life

- Access
  - Hemodialysis Fistula Maturation Study

- Dialysis procedures
  - Increase length and frequency of dialysis
  - Frequent Hemodialysis Network

- Test anti-inflammatory drugs
  - ESRD Novel Therapeutics Network

- Test novel clinical trial design
Practice influences research and research influences practice.

Ongoing, rapidly responsive, iterative process that translates into improved care for patients.

- Enroll and Randomize 400 Dialysis Units
- Usual Care
  - Extra 30 min
- Enroll 4000 New Patients
- Measure Medical Record
  - 10x more patients
  - More representative
  - 1/3 the time
  - 1/10 the cost
Prevalence of CKD in Hispanics/Latinos and non-Hispanic Whites and Blacks By Age Group
Geographic variations in adjusted prevalent rates of ESRD per million population, 2011, by HSA

All-cause rehospitalization or death within 30 days after live hospital discharge, in the general Medicare (no CKD), CKD, & hemodialysis populations, age 66+, 2011

Figure 3.1 (Volume 1)

January 1, 2011 point prevalent Medicare patients, age 66 & older on December 31, 2010, unadjusted. Includes live hospital discharges from January 1 to December 1, 2011.
Goal: Encourage basic, applied, and translational or clinical bioengineering research that could make a significant contribution to improving human health:

- Collaboration between physical and engineering sciences and biological sciences
  - 13 Institutes and Centers participate
  - Up to $2M per year in total cost
  - 5 year award with one renewal
Opportunities for Small Business Innovation Awards and Small Business Technology Transfer Awards

- Improved Biomaterials for Urinary and Dialysis Catheters (SBIR, PA-13-050) and (STTR, PA-13-051)

Goal: To support research and development of biomaterials that improve the function of catheters used for dialysis or urinary drainage
Due to Advances of Past 30 Years
Americans are Living Longer and Healthier

For the second consecutive year, annual cancer deaths in the United States have fallen.

Over 60% decrease in mortality for heart disease. Heart disease investment per American ~$4/yr 1974-2004

Life expectancy rises to 78 years, up 6 years since 1974.

Chronic elderly disability among older Americans has dropped by 30% in the past 2 decades and the rate of decline is accelerating.

Total NIH Investment per American ~$44/yr 1974-2004

Source: KG Manton et al., PNAS: 103 (48) 18374
• Identify causes or associations
• Basic-translational research
• Identify factors that promote progression
• Educate at-risk populations
• Investigate clinical interventions
Effect of eGFR

- eGFR < 30: 11.58
- 30 - < 40: 11.34
- 40 - < 50: 10.75
- 50 - < 60: 10.04
- 60 ≤ eGFR: 9.10

Aortic PWV in meters/second

Institute of Cardiovascular and Digestive Diseases