Current and Future Burden of CKD

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BUT, a better title might be
Preventing the Future Burden of CKD

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Disclosure

- I am an editor at the New England Journal of Medicine, for which I receive a salary.
- Editorial work may lead to intellectual bias.
CKD Prevalence: High and Increasing

- KNOWN FOR YEARS:
  - Trend for increased prevalence of CKD in the USA and select countries, irrespective of the calculation, implies persistent and rapid growth worldwide.

- Reported prevalence estimates across countries range broadly from approximately 2.0% to 44%.

- This broad range in prevalence exemplifies the differences in patient populations and unmet clinical, humanistic, and economic needs across the globe.

- Thus, reasons for differences are many.

CKD prevalence has increased by nearly 30% since 1990, with current prevalence estimates giving an approximate range between 8% and 16%.

Disease severity correlates with the extent of GFR reduction and albuminuria, which are used to classify the disease from CKD stage 1 (mild disease) to CKD stage 5 (severe disease).
Figure 1. Age-standardized DALY rates for each location by Socio-Demographic Index, both sexes combined, 2019. Reprinted with permission from reference 23. Global Burden of Disease 2019: GBD cause and risk summaries Chronic kidney Disease. Lancet 2020; 396: S152-3.
### Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73 m²)</th>
<th>Description and range</th>
<th>Persistent albuminuria categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>A1 Normal to mildly increased</td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
<td>A2 Moderately increased</td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
<td>A3 Severely increased</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
<td></td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td></td>
</tr>
</tbody>
</table>

- A1: Normal to mildly increased
- A2: Moderately increased
- A3: Severely increased

Green, low risk (if no other marker of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. GFR: glomerular filtration rate.
Kidney Health Issues We Often Miss

Lifespan issues!
DOHaD in General
Intrauterine Dev
Kidney Endowment
Childhood Events
Critical Periods in Human Gestation

- Preimplantation (1-2 weeks)
  - 1: Dividing zygote, implantation, and gastrulation
  - Not susceptible to teratogens

- Early Embryonic (3-5 weeks)
  - 3: CNS development
  - 4: Heart formation
  - 5: Common site of action of teratogens

- Mid-Embryonic (6-8 weeks)
  - 6: Eye development
  - 7: Heart development
  - 8: Ear development

- Late Embryonic (9-16 weeks)
  - 9: Brain development
  - 10: Ear development
  - 11: Palate development
  - 12: External genitalia development

- Early Fetal (20-36 weeks)
  - 20-36: CNS development
  - 27: Heart development
  - 28: Upper limbs development
  - 29: Eyes development
  - 30: Lower limbs development
  - 31: Teeth development
  - 32: Palate development
  - 33: External genitalia development
  - 34: Ear development

- Full Term (38 weeks)
  - 38: Kidneys development
  - Prenatal death
  - Major morphological abnormalities
  - Functional defects and minor morphological abnormalities
<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>Pregnancy</th>
<th>Lactation</th>
<th>Childhood</th>
<th>Adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors that → impaired fetal growth-undernutrition; ↑ glucocorticoids; uterine factors</td>
<td>Placenta</td>
<td>Fetus</td>
<td>Continued programming, esp. maturing immune system</td>
<td>Interactions with conventional risk factors. Importance of ACES (adverse Childhood experiences)</td>
</tr>
<tr>
<td>Maternal overnutrition → Obesity, hypercholesterolemia, diabetes, insulin resistance, proinflammatory states, increased oxidative stress</td>
<td>Placental and placentation abnormalities</td>
<td>Beneficial or harmful effects</td>
<td>Predictors of Kidney and Cardiovascular Risk</td>
<td></td>
</tr>
<tr>
<td>Factors → Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical manifestations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CKD</td>
<td>Htn, Diabetes, CVD</td>
</tr>
</tbody>
</table>

HISTORICAL DATA

Renal Failure in NICU—associated with poor renal growth
(and also decreased GFR and tubular dysfunction)

Fig. 2. Bilateral reduction in renal size is seen in this excretory urogram in a 5-year-old girl who had neonatal acute renal failure secondary to birth asphyxia. The length of the right kidney is 5 SD below the mean of normal and the length of the left kidney is 3.5 SD below the mean of normal. The reduction in renal mass is presumed to be the result of the perinatal renal insult.

Hints from Historical Data

HUS in Argentina

Group 1- complete recovery  74 pts

Group 2- Proteinuria or proteinuria and Htn, but normal Ccr  21 pts

Group 3 Low Ccr plus proteinuria or proteinuria and Htn  19 pts

Group 4 ESRD after 6-20 years  4 pts

N=118

Long-term Risk of CKD in Children Surviving Episodes of Acute Kidney Injury in the Intensive Care Unit: A Prospective Cohort Study

Cherry Mammen, MD, MHSc, Abdullah Al Abbas, MD, Peter Skippen, MD, Helen Nadel, MD, Daniel Levine, MD, J.P. Collet, MD, PhD, and Douglas G. Matsell, MD

Figure 2. Histogram plots show the distribution of patients’ (A) urine albumin-creatinine ratio (ACR), (B) estimated glomerular filtration rate (eGFR), and (C) measured GFR (mGFR). Black bars represent abnormal results.

Renal Endowment Genetic Risk (static)

Pharmacologic Intervention

Environmental Risk Factors (dynamic)

miRNA Methylation (dynamic)

Renal FxI Damage

TOD Risk
How do we find those at risk???
Examples of New Surrogate Markers

• Renal functional reserve
• Nanoparticles in diagnosis
• New biomarkers
• New imaging techniques
Examples of New Surrogate Markers

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• New imaging techniques
## Stress Tests of Kidney Function – AKA Renal Functional Reserve Test Methods

<table>
<thead>
<tr>
<th>TEST METHOD</th>
<th>ASSESSED RESPONSE</th>
<th>NORMAL RESPONSE</th>
<th>POTENTIAL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral protein or IV aa</td>
<td>Increase in GFR</td>
<td>10%-30% increase</td>
<td>Estimate of single nephron fx.</td>
</tr>
<tr>
<td></td>
<td>Change in tubular Cr. secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U/P urea conc. ratio</td>
<td>Urea countercurrent X$\Delta$</td>
<td>Urea U/P ratio ≥80 at copeptin levels of 11.9 pmol/L (IQR, 7.1-28.3)</td>
<td></td>
</tr>
<tr>
<td>Oral NH4Cl (50 mEq) and U citrate/creat</td>
<td>Normal plasma bicarb</td>
<td>Ratio 187 (IQR, 125-277) mmol/mol</td>
<td></td>
</tr>
<tr>
<td>Oral bicarb</td>
<td>H+ ion retention with normal plasma bicarb</td>
<td>3 ± 14 mmol H+ retention</td>
<td>Rx subclinical acidosis</td>
</tr>
</tbody>
</table>

Examples of New Surrogate Markers

• Renal functional reserve
• Nanoparticles in diagnosis
• New biomarkers
• New imaging techniques
Use of Nanoparticles to Diagnose (and Treat) CKD

Fig. 1. The composition and properties of nanoparticles. A) Nanoparticles can serve as colloidal dispersions or a matrix structure; B) The features of NPs can be modified by size, charge, shape, and targeting ligands including antibody, peptide and small molecule.

Use of Nanoparticles to Diagnose (and Treat) CKD

Nanoparticles applications for chronic kidney disease

Disease diagnosis
- Kidney injury biomarkers detection
- Fluorescence imaging reflecting kidney function
- MRI reflecting kidney structure

Disease treatment
- Chronic kidney disease
- End-stage renal disease
  - Kidney targeting
  - Delivery of drugs
  - Delivery of nucleic acids
  - Dialysis
  - Transplantation

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Dubin et al. *Proteomics of CKD Progression in CRIC*

**METHODS**
- **CRIC: Derivation Cohort**
  - N=3235 participants with CKD
  - N=4638 proteins
  - Discovery of individual protein-CKD progression associations
  - Machine learning used to develop proteomic risk models for CKD progression

- **ARIC: Validation Cohort**
  - N=578 participants with CKD
  - External validation of prognostic proteins
  - External validation of proteomic risk models

**RESULTS**
- 330 protein biomarkers of CKD progression discovered in CRIC in fully adjusted analyses. 23 of 40 proteins selected by effect size in CRIC validated in ARIC.

- Derivation/validation of a 65-protein risk model for 10-year CKD progression. 14 of 65 are druggable targets.

**Biological insights**
- Focus on single protein associations with largest effect sizes
- Ingenuity Pathway Analysis

**Causal inferences**
- 2-sample Mendelian randomization
  - pQTLs derived from 2 cohorts: CRIC, deCODE
  - MR performed in 3 GWAS: eGFR, Rapid 3, CKDi25

**Biological emphasis on bone morphogenetic proteins, ephrin signaling, prothrombin activation**

**8 proteins implicated as causal mediators of CKD progression**
Dubin et al. *Proteomics of CKD Progression in CRIC*

- Identified 100 circulating proteins associated with CKD
- Individual protein associations and pathway analyses led to
  - Bone morphogenic proteins, ephrin signaling, prothrombin activation
  - 65-protein risk model; 14/65 proteins are druggable; C-stat (95% CI) 0.862 (0.835-0.889)
  - Causes with 5 proteins, not previously known– EGFL9, LRP-11, MXRA7, IL-1sRII and ILT-2
- Finding protein risk markers may lead to drug development that may slow CKD progression
Examples of New Surrogate Markers

• Renal functional reserve
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• New imaging techniques
Photoacoustic imaging of kidney fibrosis for assessing pretransplant organ quality

Eno Hysi,1,2 Xiaolin He,3,4 Muhannad N. Fadhel,1,2 Tianzhou Zhang,3,4 Adriana Krizova,4,5 Michael Ordon,4,5,6 Monica Farcas,4,5,6 Kenneth T. Pace,4,5,6 Victoria Mintsopoulos,4,7 Warren L. Lee,4,7 Michael C. Kollos,1,2 and Darren A. Yuen2,3,4

https://doi.org/10.1172/jci.insight.136995
Examples of New Medications and Management

• New antihypertensive agents
• New antidiabetic medications
• New antiinflammatory drugs
• Molecular approaches
• Other
Examples of New Medications and Management

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• Other
Novel Renoprotective Antidiabetic Medications

CV benefits
- 3P/4P-MACE
  - Empagliflozin
  - Liraglutide
  - Semaglutide
  - Canagliflozin
  - Albiglutide*
  - Dulaglutide
  - Sotagliflozin*
  - Efpeglenatide

Renal benefits
- Renal impairment
  - All SGLT2 inhibitors, except sotagliflozin*
  - Dulaglutide
- Albuminuria
  - All SGLT2 inhibitors, except sotagliflozin*
  - All GLP-1 RAs

Metabolic benefits
- All GLDs improved HbA1c levels
  - Other metabolic benefits were also recorded in many CVOTs, such as reductions in weight

EASD, ADA, ACC and ESC guidelines recommend GLP-1 RAs & SGLT2i in T2D with CVD

EASD guidelines recommend SGLT2i to prevent HF risk in patients with T2D

EASD guidelines recommend GLP-1 RAs, SGLT2i, DPP-4i or TZDs to minimise hypoglycaemia risk

Agents proven to save lives in patients with T2D
- Empagliflozin
- Liraglutide
- Oral semaglutide

ACC and ESC guidelines prefer agents with a proven mortality benefit

[M] Davies et al.
https://doi.org/10.1186/s12933-022-01575-9
Examples of New Medications and Management

• New antihypertensive agents
• New antidiabetic medications
• New antiinflammatory drugs
• Molecular approaches
• Other
Figure 1. | Nrf2-GSTM1 pathway protects against oxidative stress and is a potential novel therapeutic target.
Patient-Centered Approach

- Studying representative patient groups
- Obtaining patient perspectives
- Considering all biological systems, not just the kidney
- Considering *in utero* development and childhood contributions
- Listening to patient responses continually
Figure 2 Different clinical settings linked to albuminuria development and evolution, and its adequate management.
Early Life Factors

**Clinical problem**
- Early cardiorenal risk
  - Normal
  - Novel early biomarkers
- Later cardiorenal risk
  - Target organ damage
  - eGFR
  - Renal Failure

- Albuminuria
  - Mild: UACR < 30 mg/g
  - Moderate: UACR 30-300 mg/g
  - Severe: UACR > 300 mg/g

**Solution**
- Implementation albuminuria detection

**Tentative**
- New drugs to control early stages of albuminuria: GLP1-RAs, SGLT2is, Finerenone

European Heart Journal (2023) 44, 1112–1123
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THANK YOU!

Questions?

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