OUTLINE

- Definitions of CKD
- Estimation of GFR by formulas
- Application of Definitions to the Elderly
  - Role of proteinuria (albuminuria) in diagnosis and prognosis of CKD in the elderly
- Conclusions and recommendations

Chronic Kidney Disease (CKD): Classification—(NKF-K/DOQI-2002)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Kidney Damage</th>
<th>eGFR* (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>NA</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

(*calculated from serum creatinine level by the abbreviated MDRD equation; NA= not applicable: findings must persist for ≥3 months)

KDIGO Modification (2006)

- Suffix T added to Stages 1-4 if recipient of a renal transplant
- Suffix D added to Stage 5 if receiving Dialysis

Question #1: An Elderly Woman with a “low” eGFR

- A 75 year old widow is seen by her general internist for a pre-operative evaluation connected with a planned left hip replacement for debilitating osteoarthritis and necrosis of the femoral head.
- Other than impaired vision from cataracts she feels well. There is no personal or family history of kidney disease. She takes an occasional NSAID for pain, and regular ergocalciferol and calcium supplements.
Question #1

Her physical examination reveals a thin (weight= 50 kg, height 1.6m), but otherwise healthy appearing elderly woman with a blood pressure of 140/78mmHg. There is no edema or JV distension. No abdominal bruits. Pulses are full and intact. Pain on pressure over the left hip is found.

Laboratory studies reveal a serum creatinine of 1.05mg/dL (a calculated eGFR= 54ml/min/1.73m² according to the report). Hemoglobin is 11.6gms/dl, serum albumin is 4.4g/dL, the blood sugar (fasting) is 90mg/dL and serum cholesterol is 185mg/dL. All other biochemical studies are also normal.

A urinalysis is negative for protein and blood

An EKG and chest X-Ray are normal

Based on an eGFR of 54ml/min/1.73 m² the patient is told she has Chronic Kidney Disease (CKD), Stage 3.

Which ONE of the following would you recommend now?

A. Perform metabolic investigations, including a 1,25 and 25-hydroxy Vitamin D level, parathyroid hormone
B. Order an abdominal ultrasound and CT scan
C. Refer to a Nephrologist for further evaluation of CKD
D. Reassure her that she can undergo her planned hip surgery as scheduled
E. Cancel her scheduled hip surgery

The correct answer is D– The patient has "normal" eGFR for her age and gender and does not have CKD


- Stages 1 and 2 (38% of Total)
  * 100% had abnormal albuminuria (by definition)-88% had microalbuminuria and 12% had macroalbuminuria

- Stage 3 (59% of Total)
  * 67% had no abnormal proteinuria (not needed for definition)

- Stage 4 (2.8% of Total)
  * 23% had no abnormal proteinuria

- Total Stage 1-4 (100% of total)
  * M/F ratio = 0.74
  * 87% had no abnormal proteinuria
Chronic Kidney Disease (CKD): **UK (NICE) Classification**

- **Stage 1 and 2** - Same as KDOQI
- **Stage 3** - Divided into 4 parts:
  - > Stage 3A (eGFR = 40-59 ml/min/1.73 m²)
  - > Stage 3B (eGFR = 30-39 ml/min/1.73 m²)
  - > Stages 3A/3B designated as proteinuria + (p+, UAE=>500mg/d; UACR= >0.5) or negative (p-, UAE= <500mg/d; UACR= <0.5))
- **Stage 4** - Same as KDOQI
- **Stage 5** - Same as KDOQI

*(Eight Stages total)*

---

Chronic Kidney Disease (CKD): **Kaiser-Permanente Definition**

- **Stage 1 and 2** - macroalbuminuria only; eGFR criteria same as KDOQI
- **Stage 3** - eGFR threshold= eGFR + age/2 <85 ml/min/1.73 m² but >30 ml/min/1.73 m²
- **Stage 4** - same as KDOQI
- **Stage 5** - Same as KDOQI

*(Eight Stages total)*

---

CKD Prevalence by **Modified and Standard KDOQI Criteria**

- **Stage 1** - Collapses KDOQI Stage 1 and 2 into single stage and eliminates microalbuminuria; eGFR > 5th percentile for age and gender; evidence of renal disease (urinalysis, imaging/biopsy)
- **Stage 2** - eGFR < 5th percentile for age and gender but >30 ml/min/1.73 m²; same as Stage 1 above
- **Stage 3** - eGFR 15-30 ml/min/1.73 m² (irrespective of age or gender)
- **Stage 4** - eGFR <15 ml/min/1.73 m² (not on RRT)
- **Stage 5** - Dialysis dependent

---

DEFINITIONS OF CKD

Confused? Clarity may come from an International Consensus Conference to be Held in London, UK under the auspices of KDIGO on October 3-5, 2009

---

OUTLINE

- Definitions of CKD
- *Estimation of GFR by formulas*
- Application of Definitions to the Elderly
- Role of proteinuria (albuminuria) in diagnosis’s and prognosis in the elderly
- Conclusions and recommendations
**Precision and Bias:**

**eGFR (MDRD) vs mGFR (Cin)**

(Botev, et al, CJASN 4:899-906, 2009)

- Bias (% mean difference)
- Precision (% one SD of mean)

**Classifications of CKD According to mGFR (Cedta) and eGFR (MDRD)**

(Froissart, et al. JASN, 2005)

(2095 subjects; 1995 with CKD/162 normal donors)

<table>
<thead>
<tr>
<th>mGFR</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67%</td>
<td>32%</td>
<td>0.6%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60-89</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64%</td>
<td>21%</td>
<td>0.2%</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-59</td>
<td>0.5%</td>
<td>12%</td>
<td>78%</td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>17%</td>
<td>79%</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>0</td>
<td>0</td>
<td>3.1%</td>
<td>32%</td>
<td>65%</td>
</tr>
</tbody>
</table>

**OUTLINE**

- Definitions of CKD
- Estimation of GFR by formulas
- Application of Definitions to the Elderly
- Role of proteinuria (albuminuria) in diagnosis’s and prognosis in the elderly
- Conclusions and recommendations

**Question #2- A Frail elderly lady in the ICU**

- A 66 year old woman with uro-sepsis following a liver transplant. She is small (weight 42 Kg), malnourished and frail. Scr=1.8mg/dL

- eGFR (MDRD)= 30.0ml/min/1.73m2
- eCcr (C-G)= 31.2ml/min
**Question #2**

Which ONE of the following statements MOST accurately describes the true (actual) GFR in this patient?

A. The eGFR (MDRD) and eCcr (C-G) accurately reflect her actual GFR
B. Her actual GFR is greater than either the eGFR (MDRD) or the eCcr (C-G) predict
C. Her actual GFR is less than either the eGFR (MDRD) or eCcr (C-G) predict
D. The eGFR (MDRD) is a more accurate estimation of the actual GFR
E. The eCcr (C-G) is a more accurate estimation of the actual GFR

---

**Question #2**

The correct answer is C

A 24 hour urine collection was performed to quantify the endogenous creatinine clearance

The value was 14.6ml/min

eCcr (C-G)/endogenous Ccr = 2.14

eGFR (MDRD)/endogenous Ccr = 2.05

(See Freedberg Kidney Int 766:129, 2009)

---

**Question #2**

Muscle wasting (sarcopenia) markedly reduced creatinine generation, leading to “overestimation” of Ccr (and GFR) by both eGFR (MDRD) and eCcr (C-G) formulas (which rely on Scr, age, gender (and weight) only.

The same thing will happen in pure vegetarians and the opposite will happen in highly muscular in individuals

---

**GFR (Cin) According to Age-**

(Wesson, LG, 1983)

---

**CKD:**

*eGFR in "Healthy" Caucasians by Gender*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Nijmagen Biomedical Study, 2008)
**Percentile Charts:**
*Useful for Following Progression of CKD*

- Patients who move down the percentile values (e.g. from 75th to 50th to 25th) have progressive disease, even if they remain in the same KDOQI stage.
- Patients who remain in the same percentile do not have progressive disease, even if they move to higher KDOQI stages.

**Microalbuminuria:**
*Prevalence (PREVEND, 2003) (N=40,619)*

![Microalbuminuria Graph]

**UACR with Aging**

- Lean body mass (LBM; muscle mass) decreases steadily after about age 40 years in "normal" subjects (around 2 Kg/decade).
- Urinary creatinine excretion is tightly correlated with LBM.
- At constant urinary albumin excretion rate, the urinary albumin to creatinine ratio increases with aging.

**Albuminuria:**
*Gender associated changes with Aging (Verhave JC, et al AJKD 40:436, 2002)*

![Albuminuria Graph]

**eGFR does not Correlate with UAE**

**OUTLINE**

- Definitions of CKD
- Estimation of GFR by formulas
- Application of Definitions to the Elderly
- Role of proteinuria (albuminuria) in diagnosis’s and prognosis in the elderly
- Conclusions and recommendations
In order to properly utilize eGFR or Albuminuria to “diagnose” CKD one should adjust for the effects of gender and normal aging.

Question #3
- A 68 year old woman is discovered to have Stage 3 CKD (by KDOQI-CKD Classification Criteria) following routine outpatient serum creatinine test. She is a non-smoker, has no diabetes and has no family history of heart disease.
- Laboratory Tests: FBS- 100mg/dL, Total Cholesterol 170mg/dL, Uric acid 4.3mg/dL, eGFR (MDRD) 55ml/min/1.73m2, urinalysis negative protein/blood by dipstick, urinary albumin/creatinine ratio= 7mg/gm creatinine.

Question #3
- Which ONE of the following best characterizes her risk for a subsequent cardiovascular (CV) event compared to a similar patient with an eGFR (MDRD) >60ml/min/1.73m2?
  A. She is at increased risk for a fatal/non-fatal CV event over the next 5-10 years
  B. She is at decreased risk for a fatal/non-fatal CV event over the next 5-10 years
  C. Her risk for a fatal/non-fatal CV event is neither decreased or increased

The Correct answer is C- In the absence of proteinuria (albuminuria) a low GFR (in the normal range for her age and gender) does not constitute a significant CV risk factor.

eGFR and Albuminuria in Prediction of ESRD and CVD
- Albuminuria is a better predictor of risk of ESRD and CVD events than eGFR.
- Non-albuminuric Stage 3 CKD (Stage 3A, p-) uncommonly progresses to ESRD and has a low relative risk of CVD in subjects over 65 years of age.

Hazard Ratios for ESRD by eGFR and Urinary Albumin/Creatinine Ratio (Hallan S, et al JASN April, 2009)
Change in eGFR over time in CKD


-8 -6 -4 -2 0
Change in eGFR (ml/min/1.73m²) over 4 years

- eGFR <5th percentile (13% albuminuria)
- Hematuria (5% albuminuria)
- Macroalbuminuria (15% eGFR < 5th percentile)

All-Cause Mortality and Proteinuria

(At same eGFR strata)
Taiwan Health Management Institution Study; Lancet 2008

CVD and CKD:

Cross-Classification of eGFR and Microalbuminuria: Effect on CV Event Risk

- CV Events (Hazard Ratio after adjustment for co-morbidity-95% CI)
  - Microalbuminuria
    - Absent  1.00  1.20
    - Present
  - eGFR
    - Not Reduced  1.00  1.20
    - (ref)  (0.8-1.3)
    - Reduced*  0.90  1.60
      (0.6-1.4)  (1.0-2.5)

(*) <64ml/min/1.73m² in males; <59ml/min/1.73m² in females

CKD Stage 3

Risk of Cardiovascular Disease
(Brantsma AH, et al and PREVEND. NDT, 2008)
(n=8495-1590 with CKD)

- Hazard Ratio for CV Events (see CKD<1.68)
  - Stage 1  2.0
  - Stage 2  1.5
  - Stage 3  1.0
  - Stage 3 (UAE <30mg/d)  2.5
  - Stage 3 (UAE >30mg/d)  2.0

CKD Stage

eGFR MDRD vs CVD events

(Van der Velde M, et al PREVEND/ASN 2008)

Kidney Center UMCG

eGFR (CyC), Ccr (Age > 60 years):

Kidney Center UMCG
eGFR and Diagnosis of CKD: An Illustration

- A 25 year old man with an eGFR of 55 ml/min/1.73m² is 45% below the median for his age and -25 ml/min/1.73m² below the 5th percentile for age and gender

- A 75 year old man with an eGFR of 55 ml/min/1.73m² is 30% below the median for his age and +5 ml/min/1.73m² above the 5th percentile for age and gender

**WHICH ONE HAS SIGNIFICANT CKD?**

Question #4

- Patient A – a 25 year old man with an eGFR of 55 ml/min/1.73m² (p-) is 45% below the median for his age and -25 ml/min/1.73m² below the 5th percentile for age and gender

- Patient B – a 75 year old man with an eGFR of 55 ml/min/1.73m² (p-) is 30% below the median for his age and +5 ml/min/1.73m² above the 5th percentile for age and gender

**OUTLINE**

- Definitions of CKD
- Estimation of GFR by formulas
- Application of Definitions to the Elderly
- Role of proteinuria (albuminuria) in diagnosis’s and prognosis in the elderly
- Conclusions and recommendations

**CONCLUSIONS**

- Use of eGFR alone to “diagnose” CKD leads to many false positives—particularly in elderly females
- No clear rationale for separating Stage 1 and 2 in KDOQI and NICE
- Albuminuria is a much stronger risk factor than eGFR in predicting outcome (ESRD and CVD), but values must be adjusted for age and gender

**RECOMMENDATIONS**

- New and uniform criteria, with adjustment for effects of age and gender, for “diagnosing” CKD are needed
- Assessment of Albuminuria (UACR, second morning void), adjusted for gender and age, should be used for early detection of high risk subjects (at any age) and for prediction ESRD and CVD risk.
- Prospective trials are needed to assess the cost-effectiveness of detection (screening) strategies based on albuminuria
THANK YOU

PROPOSED NEW DEFINITIONS OF CKD BASES ON eGFR and UACR CRITERIA

- **CKD-0**: No CKD - unless imaging, urinalysis or biopsy abnormal - Low Risk of CVD/ESRD
- **CKD-1**: Possible CKD - depends on Age <65 y, imaging, urinalysis or pathology abnormal - Moderate Risk of CVD/ESRD
- **CKD-2**: Definite CKD - without need for abnormal imaging, urinalysis or pathology - High Risk of CVD/ESRD

A Grid For Diagnosis and Prognosis Of Chronic Kidney Disease (CKD)

<table>
<thead>
<tr>
<th>Stage</th>
<th>A₀ (&lt;G30mg/gm)</th>
<th>A₁ (30-300mg/gm)</th>
<th>A₂ (&gt;300mg/gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G₁</td>
<td>CKD-0</td>
<td>CKD-0/</td>
<td>CKD-2</td>
</tr>
<tr>
<td>(90+)</td>
<td></td>
<td>CKD-1</td>
<td></td>
</tr>
<tr>
<td>G₂</td>
<td>CKD-0</td>
<td>CKD-0</td>
<td>CKD-2</td>
</tr>
<tr>
<td>(60-89)</td>
<td></td>
<td>CKD-1</td>
<td></td>
</tr>
<tr>
<td>G₃a</td>
<td>CKD-0/</td>
<td>CKD-1</td>
<td>CKD-2</td>
</tr>
<tr>
<td>(45-59)</td>
<td>CKD-0</td>
<td>CKD-1</td>
<td></td>
</tr>
<tr>
<td>G₃b</td>
<td>CKD-1</td>
<td>CKD-2</td>
<td>CKD-2</td>
</tr>
<tr>
<td>(30-44)</td>
<td></td>
<td>CKD-2</td>
<td></td>
</tr>
<tr>
<td>G₄</td>
<td>CKD-2</td>
<td>CKD-2</td>
<td>CKD-2</td>
</tr>
<tr>
<td>(15-29)</td>
<td></td>
<td>CKD-2</td>
<td></td>
</tr>
<tr>
<td>G₅</td>
<td>CKD-2</td>
<td>CKD-2</td>
<td>CKD-2</td>
</tr>
<tr>
<td>(&lt;15)</td>
<td></td>
<td>CKD-2</td>
<td></td>
</tr>
</tbody>
</table>

A Grid For Diagnosis and Prognosis (CVD-RR) Of Chronic Kidney Disease (CKD)

<table>
<thead>
<tr>
<th>Stage</th>
<th>A₀ (G100%)</th>
<th>A₁ (30-100)</th>
<th>A₂ (&gt;100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G₁</td>
<td>1.00</td>
<td>1.7-2.0</td>
<td>2.7-3.6</td>
</tr>
<tr>
<td>G₂</td>
<td>1.00</td>
<td>2.0</td>
<td>3.6</td>
</tr>
<tr>
<td>G₃a</td>
<td>1.3-1.7</td>
<td>2.5</td>
<td>4.1</td>
</tr>
<tr>
<td>G₃b</td>
<td>1.9-2.7</td>
<td>3.3</td>
<td>5.0</td>
</tr>
<tr>
<td>G₄</td>
<td>8.0</td>
<td>4.9</td>
<td>8.0</td>
</tr>
<tr>
<td>G₅</td>
<td>&gt;10</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Classification of CKD: The Future?

- Refinement of a G (eGFR)-A (Albuminuria) stratification (18 cells)
- Sub-stratification by Age (< or > 65 years) and Gender (M/F)
- Relative and Absolute Risks of All-Cause mortality, CVD mortality, ESRD, Progressive CKD by G-A Stage
- “Risk Scoring” by G-A Stage, modified by Age and Gender (Low, Medium, High)

Example

- 50 year old man with Autosomal Dominant Polycystic Kidney Disease; eGFR 60ml/min/1.73m², UACR 150mg/gm, bilaterally enlarged Cystic kidneys by ultrasound
- **CKD-1-G₂A₁; RR=2-3 for CVD; ADPKD**