Outpatient Prevention and Management of Declining Renal Function

Mireille El Ters
Assistant Professor of Medicine
Division of Nephrology, Mayo Clinic, Rochester
03/13/2020
Disclosure

Relevant Financial Relationships
None

Off-Label/Investigational Uses
None
Learning Objectives

• To review the different methods of evaluation of kidney function and proteinuria

• To review the definition and epidemiology of chronic kidney disease

• To discuss prevention and management of kidney disease

• To review some common nephrotoxic agents to be aware of.
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Evaluating the kidney function

Estimation of kidney function:

1-Serum Creatinine
2- Serum Cystatin C

Measurement of kidney function:

Iothalamate clearance
Evaluating the kidney function

Estimation of kidney function:

1- Serum Creatinine
2- Serum Cystatin C

Measurement of kidney function:

Iothalamate clearance (radionuclide testing)
Evaluating the kidney function

Estimation of kidney function:

1-Serum Creatinine

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most frequently used tool</td>
<td>Affected by muscle mass</td>
</tr>
<tr>
<td>Widely available and inexpensive</td>
<td>May be affected by certain medications that affect its secretion (trimethoprim)</td>
</tr>
<tr>
<td></td>
<td>Non linear relationship to GFR</td>
</tr>
</tbody>
</table>
Evaluating the kidney function

- Serum creatinine
Evaluating the kidney function

Estimation of kidney function:

2- Serum Cystatin C

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produced by all nucleated cells and freely filtered by glomeruli.</td>
<td>Less widely available</td>
</tr>
<tr>
<td>Not affected by muscle mass (helpful in patients with either too much muscles, or in old patients who have very low muscle mass: elderly, ESLD, malnourished)</td>
<td>Less widely used and as such less experience using it</td>
</tr>
<tr>
<td>May identify small changes in GFR better than creatinine</td>
<td>Levels may be affected by diabetes, thyroid disease, acute inflammation, use of steroid.</td>
</tr>
</tbody>
</table>
Evaluating the kidney function

Estimation of kidney function:

1- Serum Creatinine
2- Serum Cystatin C

I would use CKD EPI estimation with Creatinine
I would use CKD EPI with both Creatinine and Cystatin C in cases with borderline eGFR to confirm CKD

MDRD equation
CKD EPI (creatinine and/or cystatin C)
Cockcroft-Gault Equation
24 h urine Creatinine clearance
Evaluating the kidney function

Measurement of kidney function:

Iothalamate clearance:

- Has no role in primary care clinic
- Expensive and not available except in few centers
- Usually reserved for donor evaluation
Evaluation of proteinuria

• 24 h urine protein and albumin:
  - Normal protein < 150 mg/24 h
  - Normal albumin < 30 mg/24 h
  - Macro-albuminuria > 300 mg/24 h → Glomerular injury

• Spot urine testing:
  - Urine albumin/creatinine ratio: < 30 mg/g roughly equals 30 mg/24h.
  - Urine albumin: normal < 3 mg/dl
  - Urine protein/creatinine ratio
Learning Objectives

• To review the different methods of evaluation of kidney function and proteinuria

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Definition of Chronic Kidney Disease:
Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

- CKD is defined as abnormalities of kidney structure or function, present for >3 months.

Criteria for CKD (either of the following present for > 3 months)

<table>
<thead>
<tr>
<th>Markers of kidney damage (one or more)</th>
<th>Albuminuria (AER ≥ 30 mg/24 hours; ACR ≥ 30 mg/g [≥ 3 mg/mmol])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine sediment abnormalities</td>
</tr>
<tr>
<td></td>
<td>Electrolyte and other abnormalities due to tubular disorders</td>
</tr>
<tr>
<td></td>
<td>Abnormalities detected by histology</td>
</tr>
<tr>
<td></td>
<td>Structural abnormalities detected by imaging</td>
</tr>
<tr>
<td></td>
<td>History of kidney transplantation</td>
</tr>
</tbody>
</table>

| Decreased GFR                        | GFR < 60 ml/min/1.73 m² (GFR categories G3a-G5)             |

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
**Definition of Chronic Kidney Disease:**
Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

### Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

<table>
<thead>
<tr>
<th>GFR categories (ml/min per 1.73 m²)</th>
<th>Description and range</th>
<th>Persistent albuminuria categories Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 Normal or high</td>
<td>≥90</td>
<td>A1 Normal to mildly increased</td>
</tr>
<tr>
<td>G2 Mildly decreased</td>
<td>60 – 89</td>
<td>A2 Moderately increased</td>
</tr>
<tr>
<td>G3a Mildly to moderately decreased</td>
<td>45 – 59</td>
<td>A3 Severely increased</td>
</tr>
<tr>
<td>G3b Moderately to severely decreased</td>
<td>30 – 44</td>
<td></td>
</tr>
<tr>
<td>G4 Severely decreased</td>
<td>15 – 29</td>
<td></td>
</tr>
<tr>
<td>G5 Kidney failure</td>
<td>&lt;15</td>
<td></td>
</tr>
</tbody>
</table>

### Persistent albuminuria categories

<table>
<thead>
<tr>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to mildly increased</td>
<td>Moderately increased</td>
<td>Severely increased</td>
</tr>
<tr>
<td>&lt;30 mg/g &lt;3 mg/mmol</td>
<td>30 – 300 mg/g 3 – 30 mg/mmol</td>
<td>&gt;300 mg/g &gt;30 mg/mmol</td>
</tr>
</tbody>
</table>

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red, very high risk.
Prevalence of CKD stages 1-4

CKD Is Common Among US Adults

Fast Stats
- 15% of US adults—37 million people—are estimated to have CKD.*
- Most (9 in 10) adults with CKD do not know they have it.
- 1 in 2 people with very low kidney function who are not on dialysis do not know they have CKD.

*Data from the National Health and Nutrition Examination Survey (NHANES) 2011-2014

Causes of chronic kidney disease

- Diabetes: 38%
- High blood pressure: 26%
- Glomerulonephritis: 16%
- Other cause: 15%
- Unknown cause: 5%

N=726,331 (all ages, 2016)
Source: US Renal Data System
*Includes polycystic kidney disease, among other causes.

CKD risk factors: Diabetes Mellitus

Advanced Stage CKD (stages 3 and 4) Prevalence by Year and Diabetes Status in U.S. Adults
National Health and Nutrition Examination Survey

[Bar chart showing prevalence of advanced CKD stages 3 and 4 by year and diabetes status.]


*Adults aged 20 years or older with an estimated glomerular filtration rate—a measure of kidney function—between 15.59 ml/min per 1.73 m².
CKD risk factors: Diabetes Mellitus

Diabetes and Chronic Kidney Disease in the US population, 2009-2014

METHODS
NHANES 2009-2014
N = 15,765

N = 2,279

CONCLUSION Diabetes is strongly associated with albuminuria and reduced eGFR, independent of demographics and hypertension, and contributes substantially to the burden of CKD in the US.

CKD risk factors: Hypertension

Patient with HTN are 4 times more likely to have a diagnosis of CKD/ESRD
CKD risk factors: Hypertension
Frequency of monitoring albuminuria is low
CKD risk factors: Smoking


National Health and Nutrition Examination Survey

![Chart showing prevalence of smoking in CKD stages and general population](https://example.com/chart.png)

CKD Risk factors: Age/Gender/Ethnicity

- CKD is more common in people aged 65 years or older (38%) than in people aged 45–64 years (13%) or 18–44 years (7%).
- CKD is more common in women (15%) than men (12%).
- CKD is more common in non-Hispanic blacks (16%) than in non-Hispanic whites (13%) or non-Hispanic Asians (12%).
- About 14% of Hispanics have CKD.
Learning Objectives

• To review the different methods of evaluation of kidney function and proteinuria

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• To review some common nephrotoxic agents to be aware of.
Evaluation of Kidney Dysfunction

• Repeat the serum Creatinine.
• If question about validity, consider serum Cystatin C.
• If low GFR (< 60 ml/min) is confirmed:
  - Review of personal and family history (including and physical exam (BP, BMI).
  - Review of medication list.
  - Obtain urine analysis.
  - Obtain imaging of the kidneys (ultrasound).
Prevention of Kidney Function Decline

1- Recognizing reversible causes:

2- Managing irreversible risk factors and preventing further kidney function damage:
Prevention of Kidney Function Decline

1- Recognizing reversible causes:

*Pre-renal, Post-renal, intrinsic causes of kidney function decline.*

2- Managing irreversible risk factors and preventing further kidney function damage:

*HTN, DM, heart disease, liver disease.*

*Avoidance of nephrotoxic agents.*
Prevention of Kidney Function Decline

1- Recognizing reversible causes:

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2- Managing irreversible risk factors and preventing further kidney function damage:

*HTN, DM, heart disease, liver disease.*

*Avoidance of nephrotoxic agents.*
Referral to Nephrology: indication

- AKI or abrupt sustained fall in GFR.
- GFR < 30 ml/min/1.73 m2 (GFR categories G4-G5).
- Consistent finding of significant albuminuria (ACR >300 mg/g or 24 h urine albumin >300 mg) or proteinuria (PCR >500 mg/g).
- Progression of CKD (rapid progression is defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m2/yr).
- Urinary red cell casts, RBC >20 per high power field sustained and not readily explained.
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents.
- Recurrent or extensive nephrolithiasis.
- Hereditary kidney disease.
Prevention of Kidney Function Decline

1- Recognizing reversible causes:

*Pre-renal, Post-renal, intrinsic causes of kidney function decline.*

2- Managing irreversible risk factors and preventing further kidney function damage:

*HTN, DM, smoking, obesity.*

*Avoidance of nephrotoxic agents.*
Prevention of Kidney Function Decline: KDIGO 2012 Guidelines for HTN

- In both diabetic and non-diabetic adults with CKD and urine albumin excretion <30 mg/24 hours (or equivalent*) whose office BP is consistently >140mm Hg systolic or >90mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently <140mm Hg systolic and <90mm Hg diastolic. (1B)

- In both diabetic and non-diabetic adults with CKD and with urine albumin excretion of >30 mg/24 hours (or equivalent*) whose office BP is consistently >130mm Hg systolic or >80mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently <130mm Hg systolic and <80mm Hg diastolic. (2D)
Prevention of Kidney Function Decline: KDIGO 2012 Guidelines for HTN

- **ARB or ACE-I** be used in **diabetic adults** with CKD and urine albumin excretion **30–300 mg/24 hours** (or equivalent*). (2D)

- **ARB or ACE-I** be used in **both diabetic and non-diabetic** adults with CKD and **urine albumin excretion >300 mg/24 hours** (or equivalent*). (1B)
Prevention of Kidney Function Decline: KDIGO 2012 Guidelines for DM

- We recommend a target hemoglobin A1c (HbA1c) of <7.0% to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. (1A).

- We recommend not treating to an HbA1c target of <7.0% in patients at risk of hypoglycemia. (1B).

- We suggest that target HbA1c be extended above 7.0% in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. (2C)

- In people with CKD and diabetes, glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk, promoting the use of angiotensin-converting enzyme inhibition or angiotensin receptor blockade, statins, and antiplatelet therapy where clinically indicated. (Not Graded).
Better control of risk factor help decrease progression of CKD

### Time-centered Approach to Understanding Risk Factors for the Progression of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Methods</th>
<th>Stage 3a</th>
<th>Stage 3b</th>
<th>Stage 4</th>
<th>Stage 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>3682 participants from Chronic Renal Insufficiency Cohort Study</td>
<td>Median Time Spent in CKD Stages</td>
<td>Years</td>
<td>Years</td>
<td>Years</td>
</tr>
<tr>
<td>GFR 20 to 70 ml/min/1.73 m²</td>
<td>7.9</td>
<td>5</td>
<td>4.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Age 58 ± 11 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black 42%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM 48%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly controlled DM</td>
<td>1.8</td>
<td>Years less in CKD stage 3a</td>
<td>6.1</td>
<td>Years less in CKD stage 3a</td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>Years less in CKD stage 3b</td>
<td>3.3</td>
<td>Years less in CKD stage 3b</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>Years less in CKD stage 5</td>
<td>0.2</td>
<td>Years less in CKD stage 5</td>
</tr>
</tbody>
</table>

### Conclusions

There are marked variations in the time spent in the different stages of CKD based on risk factors of interest and stage of disease.

Prevention of Kidney Function Decline: Dietary interventions

Protein intake:

Lowering protein intake to **0.8 g/kg/day** in adults with diabetes (2C) or without diabetes (2B) and GFR <30 ml/min/1.73 m² (GFR categories G4-G5).

Avoiding high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression.
Prevention of Kidney Function Decline: Dietary interventions

**Salt intake:**
Lowering salt intake to \(<90\text{mmol} (<2 \text{g}) \text{ per day}\) of sodium (corresponding to 5 g of sodium chloride). (1C).

**Potassium, Phosphorus management:**
Individuals with CKD receive expert dietary advice and information in the context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated. (1B).
Prevention of Kidney Function Decline: Lifestyle interventions

• Smoking cessation.

• Weight loss to target BMI 20 to 25.

• Undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes 5 times per week).
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Prevention of Kidney Function Decline: Nephrotoxic agents

Non steroidal anti-inflammatory agents

- **Metanalysis**: A total of 14 studies from 13 publications met our inclusion criteria. There were eight cohort and three cross-sectional studies, two quality improvement intervention studies and one prospective survey, representing a total of 49,209 CKD patients.

  - Cross-sectional point prevalence of NSAID use in CKD patients ranged from 8 to 21%. Annual prevalence rates ranged from 3 to 33%.

- **Conclusions**: Evidence suggests that NSAID prescriptions/use in primary care among patients with CKD is variable and relatively high.

Prevention of Kidney Function Decline: Nephrotoxic agents

Are children with CKD prescribed potentially nephrotoxic medications by primary care physicians?

Retrospective, population-based cohort study

<table>
<thead>
<tr>
<th>Methods</th>
<th>Findings</th>
<th>Rate of nephrotoxic drug prescriptions (prescriptions per 100 person-yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data source</td>
<td>Prescriptions with ≥ 1 nephrotoxic drug</td>
<td>71</td>
</tr>
<tr>
<td>UK Clinical Practice Research Datalink 1997 - 2017</td>
<td>(95% CI 55-93)</td>
<td></td>
</tr>
<tr>
<td>1,535,816 eligible patients</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Mean Age - 9.8 yrs</td>
<td>15%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Potentially nephrotoxic medications are prescribed at higher rates to children with CKD.

Prevention of Kidney Function Decline: Nephrotoxic agents

- Herbal supplements:

Prevention of Kidney Function Decline: Nephrotoxic agents

- Herbal supplements:

<table>
<thead>
<tr>
<th>Table 3. Dietary supplements (common names) with known or potential diuretic properties (39,67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe vera</td>
</tr>
<tr>
<td>Antineoplaston</td>
</tr>
<tr>
<td>Artichoke</td>
</tr>
<tr>
<td>Asparagus</td>
</tr>
<tr>
<td>Astragalus</td>
</tr>
<tr>
<td>Birch</td>
</tr>
<tr>
<td>Bladderwrack</td>
</tr>
<tr>
<td>Bupleurum</td>
</tr>
<tr>
<td>Burdock</td>
</tr>
<tr>
<td>Copper</td>
</tr>
<tr>
<td>Corn silk</td>
</tr>
<tr>
<td>Couch grass</td>
</tr>
</tbody>
</table>
Prevention of kidney disease
Oxalate Nephropathy

• Suspect oxalate nephropathy in patients with following conditions:
  - Mal-absorptive procedure for weight loss (RYGB).
  - Other conditions requiring bowel resections with chronic diarrhea.
  - Fad diet with sudden decline in kidney function.
  - High doses of vitamin C (including in homeopathic clinic).
Kidney Biopsy
Oxalate Nephropathy

H&E stain – Numerous Intratubular Calcium Oxalates with Acute Tubular Injury
Prevention of kidney disease
Diet/Oxalate

![Graph showing oxalate levels in various foods](chart.png)
Referral to Nephrology: indication

- AKI or abrupt sustained fall in GFR.
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- Consistent finding of significant albuminuria (ACR >300 mg/g or 24 h urine albumin >300 mg) or proteinuria (PCR >500 mg/g).
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- Urinary red cell casts, RBC >20 per high power field sustained and not readily explained.
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KDIGO 2012 CKD guidelines
Referral to Transplantation: indication

• Patients with estimated GFR < 20 ml/min should be referred for kidney transplant evaluation.

• Preemptive kidney transplantation is preferable to dialysis, and confers mortality advantages especially among patients with DM.
Summary

• About 15% of US population has chronic kidney disease (CKD).

• Most of the cases of CKD are not advanced and as such managed by primary care providers.

• Control of risk factors is key: HTN, DM, obesity, smoking.

• Review of medication list, including over the counter medication is key.

• Review and adjustment of diet is key.
Thank you

elters.mireille@mayo.edu