MEDICINE REVIEW COURSE 2016
Ambulatory Management of Chronic Kidney Disease

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Objectives

- To understand a general approach to a patient with chronic kidney disease
- Awareness of the goals of therapy and complications of CKD
Case study

44 Chinese Female

Background

1. DM diagnosed 2 years ago
2. Hypertension diagnosed 2 months ago
3. Hyperlipidaemia

Referred to renal clinic for proteinuria and renal impairment

HbA1C 6.6%

UPCR 3.22 g/day

UFEME. Red cells 25, White cells 10, Epithelial 0.

Creat 163 umol/L

US, Kidneys of 11-MAR-2014:
The right kidney measures 8.4 cm.
The left kidney measures 9.4 cm.
Both kidneys are normal in size, shape and echogenicity.
No focal mass or hydronephrosis is detected.
Question 1

Which of the statements below are true?

A. The kidneys are within normal size, she is likely to have acute kidney injury and should be worked up accordingly

B. The short history of diabetes mellitus virtually excludes the possibility of diabetic nephropathy as a cause of the renal impairment

C. The presence of microscopic haematuria makes the diagnosis of underlying glomerulonephritis most likely

D. The risks of performing a renal biopsy outweighs the benefits for this patient

E. A baseline creatinine would be important to obtain to help in determining chronicity of renal impairment
Which of the statements below are true?

A. The kidneys are within normal size, she is likely to have acute kidney injury and should be worked up accordingly.

B. The short history of diabetes mellitus virtually excludes the possibility of diabetic nephropathy as a cause of the renal impairment.

C. The presence of microscopic haematuria makes the diagnosis of underlying glomerulonephritis most likely.

D. The risks of performing a renal biopsy outweighs the benefits for this patient.

E. A baseline creatinine would be important to obtain to help in determining chronicity of renal impairment.
AKI vs CKD
How to tell the difference?

- History
- Laboratory tests
- Imaging
- Histology
History

Acute illnesses
Medications/TCMs
Chronic illnesses
Family history
Social History
Baseline Creatinine
ASSESSMENT
## Classification

### GFR categories in CKD

<table>
<thead>
<tr>
<th>GFR category</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>≥90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60-89</td>
<td>Mildly decreased*</td>
</tr>
<tr>
<td>G3a</td>
<td>45-59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30-44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15-29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level.

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

### Albuminuria categories in CKD

<table>
<thead>
<tr>
<th>Category</th>
<th>AER (mg/24 hours)</th>
<th>ACR (approximate equivalent)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mg/mmol</td>
<td>mg/g</td>
</tr>
<tr>
<td>A1</td>
<td>&lt;30</td>
<td>&lt;3</td>
<td>&lt;30</td>
</tr>
<tr>
<td>A2</td>
<td>30-300</td>
<td>3-30</td>
<td>30-300</td>
</tr>
<tr>
<td>A3</td>
<td>&gt;300</td>
<td>&gt;30</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR > 2220 mg/g; >220 mg/mmol]).
### 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>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>A1</td>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
<td>A2</td>
<td>Moderately increased</td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
<td>A3</td>
<td>Severely increased</td>
</tr>
</tbody>
</table>
| G3b                           | Moderately to severely decreased |                     | <30 mg/g
| G4                            | Severely decreased    |                     | 30-300 mg/g |
| G5                            | Kidney failure        |                     | >300 mg/g |

**Green:** low risk (if no other markers of kidney disease, no CKD); **Yellow:** moderately increased risk; **Orange:** high risk; **Red:** very high risk.
Question 2

A 66 year old man with a history of diabetic nephropathy with an eGFR of 28 ml/min/1.73m² will progress to stage V CKD in

A. 1 year
B. 2 years
C. 3 years
D. 4 years
E. 5 years
A 66 year old man with a history of diabetic nephropathy with an eGFR of 28 ml/min/1.73m$^2$ will progress to stage V CKD in

A. 1 year
B. 2 years
C. 3 years
D. 4 years
E. 5 years
PROGRESSION
AND TREATMENT OF
Table 20 | Decline in kidney function in various populations (longitudinal studies only)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>N</th>
<th>GFR decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slack TK(^{216})</td>
<td>Healthy kidney donors</td>
<td>141</td>
<td>0.40 ml/min/year</td>
</tr>
<tr>
<td>Rowe JW et al.(^{217})</td>
<td>Healthy males</td>
<td>293</td>
<td>0.90 ml/min/1.73 m(^2)/year (CrCl)</td>
</tr>
<tr>
<td>Lindeman RD(^{218})</td>
<td>Healthy males</td>
<td>254</td>
<td>0.75 ml/min/1.73 m(^2)/year (CrCl)</td>
</tr>
<tr>
<td>Halbesma N et al.(^{219})</td>
<td>PREVEND cohort (all participants)</td>
<td>6894</td>
<td>0.55 ml/min/1.73 m(^2)/year</td>
</tr>
<tr>
<td>Imai E et al.(^{220})</td>
<td>Annual health exam participants in Japan</td>
<td>120,727</td>
<td>0.36 ml/min/1.73 m(^2)/year</td>
</tr>
<tr>
<td>Matsuchita K et al.(^{221})</td>
<td>Atherosclerosis Risk In Communities Cohort</td>
<td>13,029</td>
<td>0.47%/year (median)</td>
</tr>
<tr>
<td>Kronborg J et al.(^{222})</td>
<td>Healthy adults from Norway</td>
<td>4441</td>
<td>1.21 ml/min/1.73 m(^2)/year (men)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.19 ml/min/1.73 m(^2)/year (women)</td>
</tr>
<tr>
<td>Lindeman RD(^{218})</td>
<td>Males with renal/urinary tract disease</td>
<td>118</td>
<td>1.10 ml/min/year (CrCl)</td>
</tr>
<tr>
<td>Lindeman RD(^{218})</td>
<td>Males with hypertension</td>
<td>74</td>
<td>0.92 ml/min/1.73 m(^2)/year (CrCl)</td>
</tr>
<tr>
<td>Halbesma N et al.(^{219})</td>
<td>PREVEND cohort – adults with macroalbuminuria (&gt; 300 mg/24 hours)</td>
<td>86</td>
<td>1.71 ml/min/1.73 m(^2)/year</td>
</tr>
<tr>
<td>Halbesma N et al.(^{219})</td>
<td>PREVEND cohort – Adults with impaired renal function (5% lowest CrCl/MDRD GFR)</td>
<td>68</td>
<td>0.05 ml/min/1.73 m(^2)/year</td>
</tr>
<tr>
<td>Imai E et al.(^{220})</td>
<td>Annual health exam participants in Japan with hypertension</td>
<td>16,722</td>
<td>0.3 to 0.5 ml/min/1.73 m(^2)/year</td>
</tr>
<tr>
<td>Imai E et al.(^{220})</td>
<td>Annual health exam participants in Japan with proteinuria (≥1+ dipstick proteinuria)</td>
<td>2054</td>
<td>0.6 to 0.9 ml/min/1.73 m(^2)/year</td>
</tr>
<tr>
<td>Hemmelgarn B et al.(^{223})</td>
<td>Males age &gt; 65 with diabetes</td>
<td>490</td>
<td>2.7 ml/min/1.73 m(^2)/year</td>
</tr>
<tr>
<td>Hemmelgarn B et al.(^{223})</td>
<td>Males age &gt; 65 without diabetes</td>
<td>2475</td>
<td>1.4 ml/min/1.73 m(^2)/year</td>
</tr>
<tr>
<td>Hemmelgarn B et al.(^{223})</td>
<td>Females age &gt; 65 with diabetes</td>
<td>445</td>
<td>2.1 ml/min/1.73 m(^2)/year</td>
</tr>
<tr>
<td>Hemmelgarn B et al.(^{223})</td>
<td>Females age &gt; 65 without diabetes</td>
<td>3163</td>
<td>0.8 ml/min/1.73 m(^2)/year</td>
</tr>
<tr>
<td>Keller C et al.(^{224})</td>
<td>Cardiovascular Health Study</td>
<td>4128</td>
<td>1.83 ml/min/1.73 m(^2)/year (based on cystatin C-based eGFR)</td>
</tr>
</tbody>
</table>

Abbreviations: CrCl, creatinine clearance; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PREVEND, Prevention of Renal and Vascular End-Stage Disease.
Table 21 | Decline in kidney function in CKD populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>N</th>
<th>Baseline GFR ml/min/1.73 m²</th>
<th>Mean Follow-up years</th>
<th>GFR decline Mean (SD) or (95% CI) ml/min/1.73 m²/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD Study Group (^226)</td>
<td>Study A: GFR 25-80 ml/min/1.73 m²</td>
<td>28</td>
<td>Mean (SD)</td>
<td>1.2</td>
<td>3.7 (7.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37.1 (8.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study B: GFR 7.5-24 ml/min/1.73 m²</td>
<td>63</td>
<td>15.0 (4.5)</td>
<td></td>
<td>4.3 (4.7)</td>
</tr>
<tr>
<td>Klahr S et al. (^227)</td>
<td>Study 1: GFR 25-55 ml/min/1.73 m²</td>
<td></td>
<td>Mean (SD)</td>
<td>2.2 years</td>
<td>4.5 (3.7 – 5.3)</td>
</tr>
<tr>
<td></td>
<td>- Usual protein, usual MAP</td>
<td>145</td>
<td>37.6 (9.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Usual protein, low MAP</td>
<td>149</td>
<td>38.2 (8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Low protein, usual MAP</td>
<td>140</td>
<td>38.9 (8.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Low protein, low MAP</td>
<td>151</td>
<td>39.7 (9.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study 2: GFR 13-45 ml/min/1.73 m²</td>
<td></td>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Low protein, usual MAP</td>
<td>62</td>
<td>18.7 (3.1)</td>
<td></td>
<td>4.9 (3.8 – 5.9)</td>
</tr>
<tr>
<td></td>
<td>- Low protein, low MAP</td>
<td>67</td>
<td>18.8 (3.3)</td>
<td></td>
<td>3.9 (3.2 – 4.7)</td>
</tr>
<tr>
<td></td>
<td>- Very low protein, usual MAP</td>
<td>61</td>
<td>18.3 (3.7)</td>
<td></td>
<td>3.6 (2.8 – 4.4)</td>
</tr>
<tr>
<td></td>
<td>- Very low protein, low MAP</td>
<td>65</td>
<td>18.4 (3.5)</td>
<td></td>
<td>3.5 (2.6 – 4.5)</td>
</tr>
<tr>
<td>Wright J et al. (^228)</td>
<td>African Americans with hypertension and GFR 20-65 ml/min/1.73 m²</td>
<td></td>
<td>Mean (SD)</td>
<td>4 years</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td></td>
<td>- Low MAP</td>
<td>380</td>
<td>46.0 (12.9)</td>
<td></td>
<td>2.21 (0.17)</td>
</tr>
<tr>
<td></td>
<td>- Usual MAP</td>
<td>374</td>
<td>45.3 (13.2)</td>
<td></td>
<td>1.95 (0.17)</td>
</tr>
<tr>
<td>Eriksen B (^229)</td>
<td>GFR categories G3a and G3b (GFR 30-59 ml/min/1.73 m²)</td>
<td>3047</td>
<td>Median (IQR)</td>
<td>Median 3.7 years</td>
<td>Mean 1.03 ml/min/1.73 m²/year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55.1 (50.8 – 57.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jones C et al. (^230)</td>
<td>Nephrology referrals with GFR categories G3a-G5 (GFR &lt;60 ml/min/1.73 m²)</td>
<td>726</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median 0.35 ml/min/1.73 m²/year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>29 (18-38)</td>
<td>2.9 years (1.3 – 4.1)</td>
<td></td>
</tr>
<tr>
<td>Levin A et al. (^231)</td>
<td>Nephrology referrals with GFR categories G3a-G5 (GFR &lt;60 ml/min/1.73 m²)</td>
<td>4231</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Mean 2.65 ml/min/1.73 m²/year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33 ml/min/1.73 m²</td>
<td>2.6 years (1.6-3.6)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; IQR, interquartile range; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; SD, standard deviation; SE, standard error.
Glycemic control

- Clear benefit in intensive glycemic control in IDDM and early nephropathy
  - DCCT. NEJM 1993

- Unknown effectiveness or safety in intensive glycemic control in T2DM and early/late T2DMN

- No renal or mortality benefit in intensive glycemic control group; high % of hypoglycemic episodes
**BP**

**BP control**

- Target SBP <130-140 for all patients with DMN
  - Decrease CV events seen with BP <140/90 *UKPDS. BMJ 1998*
  - Fewer renal events with lower BP *ADVANCE HPT. Lancet 2007*
  - Decreased risk of doubling of serum creatinine *IDNT. NEJM 2001*
  - Lower BP targets have no clear benefit and associated with increased side effects *ACCORD. NEJM 2010*
**RAAS blockade**

- Captopril protects against deterioration in renal function in IDDM *Lewis. NEJM* 1993.

- Ramipril can reduce onset of overt nephropathy in T2DM *MICRO-HOPE. NEJM* 2000.
RAAS blockade

ARB has renal benefits with decreased risk of doubling of creatinine and time to ESRD

- T2DM with microalbuminuria

- T2DM with macroalbuminuria

- NNT to prevent overt proteinuria/doubling of creatinine is 10/15 respectively for 2/3yrs duration
RAAS blockade

ACEI vs ARB

- No difference for microalbuminuria (Telmisartan vs Enalapril) DETAIL. NEJM 2004

ARB vs ARB

- Telmisartan same as Valsartan in macro-albuminuria VIVALDI. Diabetologia 2006

- Telmisartan better than Losartan AMADEO. J Clin HPT 2007
RAAS blockade plus

- Supramaximal doses of ARB may result in further reduction of proteinuria but hyperkalaemia is a known complication. 
  Parving. KI 2005; SMART. JASN 2009

- Use of dual blockade not recommended

- Combination of ACEI and Spironolactone reduces proteinuria. Mehdi. JASN 2009

- Combination of ACEI and Alikiren controversial
  AVOID. cJASN 2007; ALTITUDE. NEJM 2012–discontinued 2011
“Even partial reduction in proteinuria reduces CKD progression”

- Atkins. AJKD 2005
Guidelines (KDIGO)

- Both diabetic and non-diabetic adults with CKD
  - and urine albumin excretion <30 mg/24 hours (or equivalent*)
    - to maintain a BP that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. (1B)
  - urine albumin excretion of ≥30mg/24 hours (or equivalent*)
    - to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. (2D)
- 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)
- Insufficient evidence to recommend combining an ACE-I with ARBs to prevent progression of CKD. (Not Graded)
- Target hemoglobin A1c (HbA1c) of ~7.0% (53mmol/mol) to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. (1A)
- People with CKD and serum bicarbonate concentrations <22 mmol/l treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range, unless contraindicated. (2B)
**On routine follow-up in the renal clinic the patient is asymptomatic and has the following laboratory results**

<table>
<thead>
<tr>
<th>Name</th>
<th>Reference Range</th>
<th>UOM</th>
<th>22-Jul-2014</th>
<th>29-Aug-2014</th>
<th>12-Nov-2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemoglobin (HB)</strong></td>
<td>11.0 - 15.0</td>
<td>g/dL</td>
<td>9.9</td>
<td>10.6</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>Iron Saturation (FESAT)</strong></td>
<td>15 - 45</td>
<td>%</td>
<td></td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td><strong>Ferritin (FER)</strong></td>
<td>12 - 307</td>
<td>ug/L</td>
<td></td>
<td>154</td>
<td>150</td>
</tr>
<tr>
<td><strong>Potassium (K)</strong></td>
<td>3.5 - 5.0</td>
<td>mmol/L</td>
<td>4.8</td>
<td>4.9</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Creatinine (CRE)</strong></td>
<td>40 - 75</td>
<td>umol/L</td>
<td>317</td>
<td>329</td>
<td>474</td>
</tr>
<tr>
<td><strong>eGFR (EGFRF)</strong></td>
<td></td>
<td></td>
<td>14</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td><strong>Urea (URE)</strong></td>
<td>2.9 - 9.3</td>
<td>mmol/L</td>
<td></td>
<td>18.2</td>
<td>25.3</td>
</tr>
<tr>
<td><strong>Bicarbonate (CO2)</strong></td>
<td>19 - 31</td>
<td>mmol/L</td>
<td></td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td><strong>Calcium, Adjusted (CAC)</strong></td>
<td>2.15 - 2.58</td>
<td>mmol/L</td>
<td></td>
<td>2.4</td>
<td>2.28</td>
</tr>
<tr>
<td><strong>Phosphate (PO4)</strong></td>
<td>0.8 - 1.6</td>
<td>mmol/L</td>
<td></td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>PTH, (intact) (PTHI)</strong></td>
<td>0.8 - 6.8</td>
<td>pmol/L</td>
<td></td>
<td>58.8</td>
<td>56.5</td>
</tr>
</tbody>
</table>
Question 3

Which of the following statements are false?

A. She should be referred for dialysis counselling

B. She will benefit from an erythropoietin stimulating agent

C. She has secondary hyperparathyroidism and should be started on a vitamin D analogue once her phosphate is reduced

D. In view of her eGFR of <15 she should be initiated on dialysis immediately

E. Her ACEI/ARB should be stopped
Which of the following statements are false?

A. She should be referred for dialysis counselling

B. She will benefit from an erythropoietin stimulating agent

C. She has secondary hyperparathyroidism and should be started on a vitamin D analogue once her phosphate is reduced

D. In view of her eGFR of <15 she should be initiated on dialysis immediately

E. Her ACEI/ARB should be stopped
COMPLICATIONS
AND MANAGEMENT OF
ANAEMIA
CKD-MBD
ACIDOSIS
NUTRITION
Anaemia

- Hb should be maintained at 10-11mg/dl
- No necessity to initiate ESA therapy is Hb is $\geq 10$ mg/dl
  - *KDIGO 2012*
    - No difference in CV events and all cause mortality, LVMI or decline in GFR.
  - *CREATE. NEJM 2006*
    - Higher hazard ratio of composite death and trial was terminated for presumed futility.
  - *CHOIR. NEJM 2005*
    - No difference in QOL or death but an increased in cancer related death, CVAs and VTEs in Darbepoietin group.
  - *TREAT. NEJM 2009*
**CKD-MBD**

- Monitoring of calcium, phosphate, PTH and ALP
- BMD not recommended if eGFR <45 ml/min/1.73m²
- Maintain serum phosphate in normal range, optimal PTH level is not known
- Bisphosphonates not recommended if eGFR <30 ml/min/1.73m²
ACIDOSIS

• Serum bicarbonate concentrations <22 mmol/l to be treated with oral bicarbonate supplementation to maintain serum bicarbonate within normal range, unless contraindicated
  – KDIGO 2012

• Slows renal progression and improves nutritional status
  – De Brito-Ashurst. JASN 2009
NUTRITION

• Protein intake
  – Suggest lowering protein intake to 0.8 g/kg/day in adults with diabetes (2C) or without diabetes (2B) and eGFR <30 ml/min/1.73m²

• Salt intake
  – <90 mmol (<2g) per day of sodium in adults

• Low potassium and phosphate diet
Take home messages

• If in doubt investigate and treat as per AKI

• Counselling has a significant role in management
  – Diet
  – Medication
  – Role of Renal replacement therapy

• A holistic approach is key

• Read the KDIGO 2012 guidelines
References