Primary Care Toolkit
Understanding Diabetic Kidney Disease

Karen Jenkins  Consultant Nurse
Learning Outcomes

• To increase knowledge and understanding of:
  – Connection between Diabetes and CKD
  – Monitoring of kidney function (NICE guidance)
  – Slowing progression
  – Referral to Renal Team
  – Medicines management (Hypertension, oral glycaemics, cardio vascular risk)
  – Managing diabetes specifically when having haemodialysis
Who should be screened for CKD?

- People with the following conditions should be screened for CKD:
  - Diabetes
  - Hypertension
  - Acute kidney injury
  - Cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease)
  - Known structural renal tract disease, recurrent renal calculi or prostatic hypertrophy
  - Prescribed drugs that have an impact on kidney function, e.g. calcineurin inhibitors, lithium, NSAIDs
## Causes & Risk Factors of CKD

### Causes
- Type 1 or type 2 diabetes
- Hypertension
- Glomerulonephritis
- Interstitial nephritis
- Autosomal dominant polycystic kidney disease (ADPKD)
- Prolonged obstruction of the urinary tract, e.g., enlarged prostate, kidney stones, and some cancer
- Vesicoureteral reflux, (urine forced back into the kidneys when the bladder contracts)
- Recurrent kidney infection

### Risk Factors
- Diabetes
- Hypertension
- Cardiovascular disease
- Smoking
- Obesity
- Race: African-American, Native American, or Asian-American
- Family history of kidney disease
- Abnormal kidney structure
- Older age
Diagnosing CKD

- Symptoms
  - Often asymptomatic, disease only identified once a routine blood or urine test detects a possible problem
    - Symptoms: weight loss, poor appetite, oedema, shortness of breath, tiredness, haematuria frequency of micturition, insomnia, muscle cramps, nausea, headaches

Two eGFR estimations <60ml/min/1.73m² over a period of at least 90 days (with or without markers of kidney damage) or Normal eGFR with albumin:creatinine ratio (ACR) >3 mg/mmol
Algorithm: Screening for Proteinuria

Urine dipstick for protein
(a) Type 1: 5 years after diagnosis or earlier in the presence of other cardiovascular risk factors
(b) Type 2: at the time of diagnosis

NEGATIVE

POSITIVE
(urine protein > 30mg/mmol) on 2 separate occasions (exclude other causes e.g. UTI, CCF etc.)

Screen for microalbuminuria on early morning spot urine

NEGATIVE

Screen for microalbuminuria on early morning spot urine

NEGATIVE

Annual test

POSITIVE

Retest twice in 3–6 months (exclude other causes e.g. UTI)

If 2 of 3 tests are positive, diagnosis of microalbuminuria is established
3–6 monthly follow-up of microalbuminuria

Overt nephropathy
Quantify excretion rate e.g. 24-hr urine protein

* Optimize glycaemic control
* Strict BP control
* ACEI/ARB
* Stop smoking
* Lifestyle modification
* Treat hyperlipidaemia
** Monitor renal function
* Monitor for other diabetic end organ damage

Annual test
# Categories of Proteinuria

<table>
<thead>
<tr>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to mild ↑ &lt;3mg/mmol</td>
<td>Moderate ↑ 3-30mg/mmol</td>
<td>Severe ↑ &gt;30mg/mmol</td>
</tr>
</tbody>
</table>

## Factors that may affect ACR results

- Poor glycaemic control
- Poor blood pressure control
- Exercise
- Gender
- Race

ACR >70 REFER
Managing proteinuria

• Early identification of proteinuria can limit progression of CKD

• How to measure
  – ACR (albumin creatinine ratio)
  – PCR (protein creatinine ratio)
  – Reagent strips detect albumin not protein so not quantitative

Normalized albuminuria, Microalbuminuria, – Macroalbuminuria - old terminology

• NICE recommend ACR in preference to PCR, because it has greater sensitivity for low levels of proteinuria.
NICE CG182 CKD guidelines

Reviews and monitoring:

- Agree the frequency of monitoring (eGFR creatinine and ACR) with the person with, or at risk of, CKD; bear in mind that CKD is not progressive in many people.
- Use the table shown to guide the frequency of GFR monitoring for people with, or at risk of CKD.
- The frequency of monitoring should be tailored to the individual, according to:
  - The underlying cause of CKD
  - Past patterns of eGFR and ACR
  - Comorbidities
  - Changes to their treatment
  - Intercurrent illness
  - Whether they have chosen conservative management of CKD

### The numbers in this table indicate recommended frequency of monitoring per year

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²), description and range</th>
<th>ACR categories (mg/mmol), description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 &gt;90 Normal and high</td>
<td>A1 &lt;3 Normal to mildly increased</td>
</tr>
<tr>
<td>G2 60-89 Mild reduction related to normal range for a young adult</td>
<td>A2 3-30 Moderately increased</td>
</tr>
<tr>
<td>G3a 45-59 Mild-moderate reduction</td>
<td>A3 &gt;30 Severely increased</td>
</tr>
<tr>
<td>G3b 30-44 Moderate-severe reduction</td>
<td></td>
</tr>
<tr>
<td>G4 15-29 Severe reduction</td>
<td></td>
</tr>
<tr>
<td>G5 &lt;15 Kidney failure</td>
<td></td>
</tr>
</tbody>
</table>

### ACR categories (mg/mmol), description and range

- A1 <3 Normal to mildly increased
- A2 3-30 Moderately increased
- A3 >30 Severely increased

Reference:

Untreated diabetic kidney disease leads to kidney failure

- Without specific interventions, 20-40% of people with type 2 diabetes with albuminuria progress to overt kidney disease\(^1\)

**Insulin resistance**

**Arterial hypertension**

**Early glomerular damage**

**Increasing albuminuria**

**Structural Changes**

**Chronic kidney failure**

References:
Statistics

- An estimated 40% of patients with T2DM have some form of CKD; 18 – 30% have CKD stage 3 – 5
- The proportion of T2DM patients with kidney disease is increasing
  - The prevalence of Stage 3 – 5 CKD in T2DM patients from 12 European countries is projected to rise by approximately 50% between 2012 and 2025
- Markers of diabetic kidney disease (declining eGFR and proteinuria) are associated with
  - Increased mortality
    - Patients with T2DM and kidney disease have a higher mortality rate than those without kidney disease
    - CKD accounts for 11% of all deaths in T2DM patients
  - Renal events
  - CV events
  - CV death
Benefits of Glycaemic Control in Diabetic Kidney Disease

• Reduces rates of renal function decline
  – Particularly if combined with blood pressure control
  – Can reverse hyper-filtration and glomerular hypertrophy
  – Can delay development of albuminuria and overt kidney disease
  – Can slow down the progression of established renal insufficiency

• Reduces complications
  – Autonomic neuropathy, fluid overload

• Improves outcomes
  – Delays the need for dialysis, improves the chances of a successful transplant

• Reduces costs
  – Care for a patient on dialysis costs the NHS around £27,000 a year, while the cost of slowing down kidney deterioration is around £235 a year\(^1\)

• Optimise glycaemic control <48mmol

HbA1c: factors that influence targets

- Haemoglobin A1c (HbA1c) measures circulating Hb and glucose over a 120-day cycle
- HbA1c:
  - Normal level <42mmol
  - Impaired Glucose Tolerance 42–48mmol
  - Diabetes diagnosed > 48mmol
- Measured by three different elements
  - Amount of Hb found in reticulocytes when they leave the bone marrow.
  - Rate of Hb glycation as the red cells age. This is a specific function of the amount of glucose that Hb is subjected to.
  - The average age of the red cell
How does anaemia affect HbA1c readings?

- RBC lifespan shortened by anaemia
- CKD shortened erythrocyte survival (90 days)
- Falsely lowers HbA1c results (regardless of which assay is used)
- Iron replacement therapy also lowers HbA1c and fructosamine concentrations
- Caution when interpreting A1c and management of glycaemia when based on this measurement alone
- Suggest use of home blood glucose monitoring for these patients
Hypoglycaemia with type 2 diabetes and CKD when taking oral glucose control therapies

- Progressive CKD increases the risk of hypoglycaemia
- Risk of ‘hypos’ more difficult to predict in these patients
- Drug clearance is variable with ↓eGFR
- Symptoms of ‘hypos’ are often reduced

ALWAYS ASK ABOUT HYPOGLYCAEMIA

- Assess ‘risk and treatment’ of hypoglycaemia
- More tailored dosing is required
- Patients need to be monitored more frequently

Perform frequent therapy reviews, especially if patient commences dialysis
# Type 2 medication - considerations

<table>
<thead>
<tr>
<th>MEDICATION GROUP</th>
<th>DRUGS IN CATEGORY</th>
<th>INSTRUCTIONS IN RENAL IMPAIRMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Caution in eGFR 30-45&lt;br&gt;Stop when eGFR &lt;30 (or before if gradual decline)&lt;br&gt;Not recommended on dialysis</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>Gliclazide, Glimepiride, Glipizide</td>
<td>Caution in eGFR 30-45&lt;br&gt;Stop when eGFR &lt;30 (or before if gradual decline)&lt;br&gt;Not recommended on dialysis</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Pioglitazone</td>
<td>Considered safe in eGFR down to 15 – but consider other co-morbidities&lt;br&gt;Not recommended on dialysis</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>Linagliptin</td>
<td>No dose reduction, down to eGFR of 15</td>
</tr>
<tr>
<td></td>
<td>Alogliptin, Sitagliptin, Saxagliptin, Vildagliptin</td>
<td>Dose adjustment required (look at individual drugs)</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Lixisenatide, Byetta, Victoza, Bydureon, Dulaglutide.</td>
<td>Stop when eGFR &lt;30&lt;br&gt;Not recommended on dialysis</td>
</tr>
<tr>
<td>Sodium glucose co-transporter 2 inhibitors (SGLT-2)</td>
<td>Dapaglifozin, Canaglifozin, Empaglifozin</td>
<td>New evidence from CREDENCE (eGFR ≥ 60)&lt;br&gt;reviewing license in CKD&lt;br&gt;Not recommended on dialysis</td>
</tr>
</tbody>
</table>
Nice metformin

In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m²:

Stop metformin if the eGFR is below 30 ml/minute/1.73m².

Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m². [2015]
Optimal care for Diabetic Nephropathy

- Control blood pressure (BP)
- Control blood glucose
- Measure proteinuria
- Measure kidney function
- Assess cardiovascular risk
- Identify progressive disease and refer if appropriate
- Annual eye & foot checks
- Lifestyle advice
Referral to Kidney Doctors

- eGFR < 30ml/min with or without Diabetes
- ACR ≥ 70 mg/mmol, unless known to be caused by diabetes and already appropriately treated
- Sustained ↓ GFR of ≥25% change in GFR category or sustained ↓ GFR of ≥15 ml/min/1.73 m²
- ↓ eGFR of >25% after starting ACEi or ARB
- hypertension that remains poorly controlled using at least 4 antihypertensive drugs at therapeutic doses
- Known or suspected rare or genetic causes of CKD
- Suspected renal artery stenosis.
KEEP CALM AND FOCUS ON THE BASICS
Blood pressure management in type 2 diabetes

• Step 1
  • ACE inhibitor
    ◦ or ACE inhibitor + diuretic/CCB for people with African or Caribbean family origin
    ◦ or CCB if pregnancy is a possibility
    ◦ or ARB if intolerant to ACE inhibitors

Step 2
  Add diuretic/CCB
  ◦ If target is still not met with dual therapy, add CCB (if diuretic already added), or diuretic (if CCB already added)

Step 3
  Add alpha blocker/beta blocker/potassium-sparing diuretic
  ◦ Caution advised when giving potassium-sparing diuretic if patient already taking ACE inhibitor/ARB

Monitor every 4 – 6 months if patients have reached and maintained their target BP
  ◦ Check for possible adverse events related to anti-hypertensive medication, e.g. hypotension

If 4 or more anti-hypertensive drugs
Refer to Nephrologist
Hypertension: choice of agents

- ACE-I (or ARB if intolerant to ACE-I) first line
  - CKD (eGFR≤59), diabetes and proteinuria (ACR>3mg/mmol)
  - CKD and proteinuria (ACR>30mg/mmol)
  - People < 55yrs (regardless of proteinuria)

- Calcium channel blocker first line
  - People > 55yrs without proteinuria
  - Black people of any age without proteinuria

- Aim systolic blood pressure <140 mmHg (target range 120–139 mmHg) diastolic <80mmHg
  - SBP <130 mmHg (target range 120–129 mmHg)
  - DBP <80 mmHg

References:
Haemodialysis and Diabetes Management
What are the challenges?

**Diabetes**

- Glycaemic control
- Medication adjustment
  - Insulin
  - Oral glycaemics
- Maintaining patient self-management
  - Lifestyle changes
- Who’s job is it?

**Impact of HD**

- HD causes associated fluid shifts, metabolite and electrolyte changes
- Affects Pharmacokinetics of insulin and oral agents
- Renal gluconeogenesis is reduced in ESRF
- Insulin resistance, exacerbated by HD
- Impact of gastroparesis, malnutrition
- Timing of dialysis shifts
  - Eating patterns, long journey times to attend dialysis centres
- HbA1c unreliable
  - Renal Anaemia
Dialysis affects glycaemic control

- Affects insulin secretion, clearance and resistance (periodic improvement in uraemia, acidosis and phosphate metabolism)
- Glucose concentration in dialysate may influence glucose control
  - lower glucose dialysates associated with hypoglycaemia
- Blood glucose falls during a haemodialysis, commonly lowest point being during 3rd hour
- Glucose control on dialysis days may differ to non-dialysis days, leading to unpredictable glucose levels, and glycaemic variability.
Guidelines & HbA1C

HbA1C Targets

- ESRD HbA1c 58-68mmol/mol, (7%-8.2%) ¹
- Higher risk of hypoglycaemia in patients with poor nutrition, low albumin and low BMI
- If taking hypoglycaemia inducing agent consider HbA1c <58 mmol/mol (7.5%) particularly sulphonylureas or insulin²

Practical Tips

- Timing of dialysis patients may require snacks
- Patients with gastroparesis are encouraged to have a small meal size but frequent intake.
- A low-fat/low-fibre meal recommended to manage gastroparesis¹
- Adjust insulin administration times/doses

## Adjusting Oral Anti-Glycaemic therapy

<table>
<thead>
<tr>
<th>Medication Group</th>
<th>Drugs in this category</th>
<th>Instructions in renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Not recommended for those on dialysis</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>Gliclazide, Glimepiride, Glipizide, Glibenclamide, Tolbutamide</td>
<td>Not recommended for those on dialysis</td>
</tr>
<tr>
<td>Alpha glucoside antagonist</td>
<td>Acarbose</td>
<td>Not recommended for those on dialysis</td>
</tr>
<tr>
<td>Thiazolidinedione,</td>
<td>Pioglitazone</td>
<td>Not recommended for those on dialysis, and may increase oedema.</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>Linagliptin, Alogliptin, Sitagliptin, Saxagliptin, Vildagliptin</td>
<td>Linagliptin requires no dose reduction&lt;br&gt;The following are not recommended for those on dialysis- may be used with caution on individual patient basis&lt;br&gt;Alogliptin – reduce to 6.25mg&lt;br&gt;Sitagliptin – reduce to 25mg&lt;br&gt;Saxagliptin – reduce dose to 2.5mg&lt;br&gt;Vildagliptin – reduce dose to 50mg</td>
</tr>
<tr>
<td>GLP-1 receptor agonists/mimetics</td>
<td></td>
<td>Not recommended for those on dialysis</td>
</tr>
<tr>
<td>Sodium glucose co-transporter 2 inhibitors (SGLT-2)</td>
<td>Dapagliflozin, Canagliflozin, Empagliflozin</td>
<td>Not recommended for those on dialysis</td>
</tr>
<tr>
<td>Short-acting oral insulin secretagogues</td>
<td>Nateglinide, Repaglinide:</td>
<td>GFR&lt;30ml/min – (Stages G4 &amp; G5) – use with caution and initiate small starting. risk of hypoglycaemia patients should monitor blood glucose frequently</td>
</tr>
</tbody>
</table>
# Adjusting Insulin

<table>
<thead>
<tr>
<th>Insulin Group</th>
<th>Time of onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Renal Advice (JBDS, 2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate (Human or Animal) Isophane</td>
<td></td>
<td></td>
<td></td>
<td>Reduce dose by 25% on the morning of dialysis</td>
</tr>
<tr>
<td>Given OD or BD</td>
<td>1-2hrs</td>
<td>6-8hrs</td>
<td>16-22hrs</td>
<td></td>
</tr>
<tr>
<td>Short Acting (Human or Animal) Soluble</td>
<td></td>
<td></td>
<td></td>
<td>If am dialysis reduce breakfast dose by 10-15%</td>
</tr>
<tr>
<td>Given 30-45 mins prior to a meal</td>
<td>45 – 75 minutes</td>
<td>2-3hrs</td>
<td>6-8hrs</td>
<td>If pm dialysis reduce lunchtime dose by 10-15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>If evening dialysis reduce evening insulin by 10-15%</td>
</tr>
<tr>
<td>Human or Animal Mixed Insulin</td>
<td></td>
<td></td>
<td></td>
<td>If am or pm dialysis reduce breakfast dose by 10-15%</td>
</tr>
<tr>
<td>Given BD 30- 45 mins before meal</td>
<td>45 – 75 minutes</td>
<td>2-4hrs</td>
<td>16-22hrs</td>
<td>If evening dialysis reduce evening dose by 10-15%</td>
</tr>
<tr>
<td>Long Acting (Analogue) basal insulin</td>
<td>Continuous</td>
<td>Little or no peak</td>
<td>16 - 36hrs</td>
<td>Reduce dose by 25% on the morning of dialysis</td>
</tr>
<tr>
<td>Once or twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid Acting Analogue</td>
<td></td>
<td></td>
<td></td>
<td>If am dialysis reduce breakfast dose by 10-15%</td>
</tr>
<tr>
<td>With meals</td>
<td>5-15minutes</td>
<td>1.5 - 2hrs</td>
<td>4-5hrs</td>
<td>If pm dialysis reduce lunchtime dose by 10-15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>If evening dialysis reduce evening insulin by 10-15%</td>
</tr>
<tr>
<td>Mixed Analogue Insulin</td>
<td></td>
<td></td>
<td></td>
<td>If am or pm dialysis reduce breakfast dose by 10-15%</td>
</tr>
<tr>
<td>With meals</td>
<td>5-15minutes</td>
<td>1.5 - 2hrs</td>
<td>12-16hrs</td>
<td>If evening dialysis reduce evening dose by 10-15%</td>
</tr>
</tbody>
</table>

Adapted from SPC information
Considerations for Practice

- Possible reduction of insulin doses during and immediately following dialysis
  - Individualise on basis of Continuous Glucose Monitoring (CGM) data
- Encourage self-monitoring of blood glucose on dialysis and non-dialysis days
- Education on adjusting insulin doses to avoid hypoglycaemia
  - Different insulin’s work in different ways so the diabetes team should be involved with patients who are on dialysis and need support in managing their doses
- Those with type 2 DM may experience frequent hypoglycaemic episodes resulting in a temporary or permanent cessation of their anti-diabetic therapies
- Joint working between disciplines (diabetes/renal)
- Around 70% patients will require less insulin as kidney function declines
- Around 25% may stop insulin completely
- Action profiles are generally prolonged and less predictable
- Avoid longer-acting analogues unless there are no issues
- TDS pre-mix regimens maybe better tolerated
- Mean glucose is lower on dialysis days
- Frequent monitoring is advised
- Haemodialysis affects glycaemic control
- Pharmacokinetics of insulin & oral agents affected
Summary Key Points

• Remember the basics
• Screen for proteinuria
  – REFER appropriately
• ACE inhibitor or ARB therapy improves outcomes - BUT NOT PRESCRIBED TOGETHER
• Presence of diabetic kidney disease implies generalised vascular disease which requires holistic management
• Oral hypoglycaemic therapy needs adjusting in people with diabetic kidney disease
• Insulin may need adjusting if people with diabetes and kidney disease are receiving dialysis
• Consider referral to a Nephrologist
• Work collaboratively with your local Renal team
Thank you for listening