Great Western Hospitals NHS
NHS Foundation Trust

Swindon Diabetes Guidelines:
Management of Chronic Kidney Disease Associated with Diabetes Mellitus

Authors: Dr Tanaji Dasgupta (Consultant Nephrologist) and Dr Vladimir Vaks (Consultant Endocrinologist), 26 September 2017. To be reviewed 26 September 2022

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Executive Summary

- Patients with diabetes should be screened on an annual basis for nephropathy: In individuals with type 1 diabetes, screening for nephropathy should start 5 years after diagnosis of diabetes. In patients with type 2 diabetes, screening should begin at initial diagnosis since the exact onset of diabetes is often unknown.

- The earliest sign of kidney involvement is abnormal amounts of albumin excretion in the urine which is assessed by laboratory measurement of the albumin creatinine ratio (ACR) by which individuals can be categorized into the stages of proteinuria. Decline in filtration function of the kidney (assessed by an estimated GFR ie eGFR) usually follows this development of albuminuria. These two variables allow classification by stage of chronic kidney disease (CKD Stage).

- Treatment using recommended therapies in directed at reducing renal progression and vascular risk in integration with the management of diabetes and other associated complications.

- Patients diagnosed with diabetic kidney disease should be monitored as per existing national guidelines to detect progression.

- This guideline is designed to be used in concert with the other diabetes-related guidelines as part of integrated and individualised approach towards the management of patients.

How to Screen for Diabetic Nephropathy

What to Measure

- Measurement of urinary ACR in a first-pass morning urine sample to be sent to the Great Western Hospital biochemistry department.
- Measurement of serum creatinine and estimation of GFR (which is reported by the laboratory automatically following measurement of serum creatinine using the CKD Epi GFR formula).

Frequency of Monitoring

- This depends on the stage of CKD and frequency of monitoring is suggested in NICE Guidelines as per Table 1 below.
- Patients with G1 and G2 should have annual review of their renal status
- Patients with G3 should have 6 monthly assessment of their renal status and review of their medication to ensure that prescription of potentially nephrotoxic drugs is avoided as much as possible
- Patients with G4 and G5 should be referred to nephrology for an assessment
- Patients with G5 should also be under the care of the Diabetes Specialist Team and have access to diabetes specialist nurse support

How to approach an elevated ACR measurement

- Should be confirmed in the absence of urinary tract infection with 2 additional first-void specimens collected during the next 3 to 4 months.
- Request a specimen on a subsequent visit if UTI prevents analysis.
- Take the result to be confirming microalbuminuria if a further specimen (out of two more) is also abnormal (> 2.5 mg/mmol for men, > 3.5 mg/mmol for women)
- Identify potential false positives: fever, exercise, haematuria, infection.
- If the initial ACR is >70mg/mmol a repeat sample need not be tested.
- Microalbuminuria: defined as an ACR between 3 -30 mg/mmol
- Macroalbuminuria (proteinuria) is defined as an ACR > 30 mg/mmol

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Table 1. Frequency of monitoring of GFR (number of times per year, by GFR and ACR category) for people with, or at risk of, CKD

GFR categories (ml/min/1.73 m²), description and range	ACR categories (mg/mmol), description and range		
	A1 <3 Normal to mildly increased	A2 3–30 Moderately increased	A3 >30 Severely increased
G1 ≥90 Normal and high	≤1	1	≥1
G2 60–89 Mild reduction related to normal range for a young adult	≤1	1	≥1
G3a 45–59 Mild–moderate reduction	1	1	2
G3b 30–44 Moderate–severe reduction	≤2	2	≥2
G4 15–29 Severe reduction	2	2	3
G5 <15 Kidney failure	4	≥4	≥4

Increased risk

Increased risk

GFR=glomerular filtration rate. ACR=albumin:creatinine ratio.
Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International* (Suppl. 3): 1-150.

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Significance of Albuminuria in Diabetic Kidney Disease

- Albuminuria is an independent risk factor for cardiovascular disease and progression in renal disease. (Table 2) .
- Reduction in albuminuria is a viable target and aggressive targeted control of multiple risk factors is the corner stone of management.
- Patients with any degree of proteinuria should **be offered treatment with an ACE inhibitor or angiotensin receptor blocker (ARB) regardless of the initial blood pressure.**

Salient Points about estimated GFR (eGFR) and Staging of Chronic Kidney Disease

- Use a creatinine based estimate of GFR
- Interpret eGFR with caution at extremes of muscle mass
- In new cases of reduced eGFR confirm by retesting within 2 weeks
- Urgent despatch and testing of blood minimises incorrect results
- Metformin should not be started if eGFR <45, and should be stopped if eGFR <30
- Chronic Kidney Disease is staged according to the estimated Glomerular Filtration Rate (eGFR) and ACR (Table 2).
- Diabetic Nephropathy is characterised by the excretion of abnormal amounts of albumin in the urine, arterial hypertension and progressive decline in kidney function.

Considering Aetiology of Chronic Kidney Disease

- CKD may be attributable to diabetes if microalbuminuria is present in the presence of diabetic retinopathy in type 1 diabetes of at least 10 years' duration
- Albuminuria may be present at the time of diagnosis of type 2 diabetes mellitus.
- Other cause(s) of CKD should be considered in the presence of any of the following circumstances:
    - Absence of diabetic retinopathy
    - Rapidly decreasing GFR
    - Rapidly increasing proteinuria or nephrotic syndrome
    - Refractory hypertension
    - Presence of active urinary sediment
    - Signs or symptoms of other systemic disease
    - >30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB.

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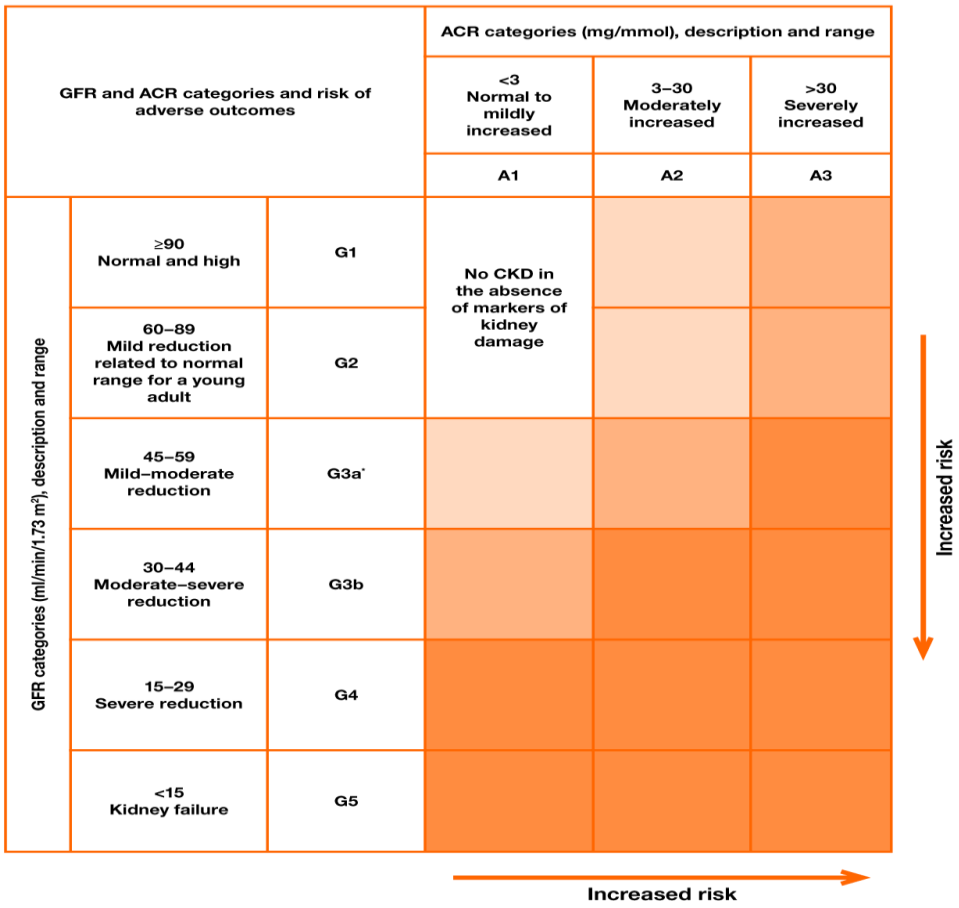

*Consider using eGFRcystatinC for people with CKD G3aA1
ACR=albumin:creatinine ratio. CKD=chronic kidney disease. GFR=glomerular filtration rate.
Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International* (Suppl. 3): 1-150.

Table 2. CKD classification

Assessment of a patient with Chronic Kidney Disease Associated with Diabetes Mellitus

- Take a full history and review list all current and past medications.
- Physical examination including evaluation for presence of cardiovascular disease.
- Specific review of blood pressure including ambulatory readings where feasible.
- Urine analysis (urine dipstick AND Albumin Creatinine Ratio), assess kidney function (eGFR), full Blood Count to assess for anaemia, kidney imaging studies if relevant, and other investigations informed by history and clinical examination
- Look for presence of retinopathy, peripheral vascular disease, other diabetes complications including neuropathy and infections.
- The presence of haematoproteinuria in the absence of infection, red cell casts on urine microscopy, vasculitic symptoms such as a rash, arthralgia or epistaxis / new sensorineural deafness, sudden nephrotic symptoms or nephrotic range proteinuria, or rapid deterioration in GFR in the absence of long standing diabetes should raise suspicion of non-diabetic kidney disease: Discuss with and refer to nephrology for advice/management, specifying your reasons for doing so.

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- Agree a plan to establish the cause of CKD during an informed discussion with the person with CKD, particularly if the cause may be treatable (for example, urinary tract obstruction, nephrotoxic drugs or glomerular disease).
- Use the person's GFR and ACR categories to assess their risk of adverse outcomes (for example, CKD progression, acute kidney injury, all-cause mortality and cardiovascular events) and use this information in discussion with the patient to inform further monitoring and management.

- **Offer a renal ultrasound scan to all people with CKD who:**

    - have accelerated progression of CKD
    - have visible or persistent invisible haematuria
    - have symptoms of urinary tract obstruction
    - have a family history of polycystic kidney disease and are aged over 20years
    - have a GFR of less than 30ml/min/1.73m^2 (GFR category G4 or G5)
    - are considered by a nephrologist to require a renal biopsy

- Advise people with a family history of inherited kidney disease about the implications of an abnormal result before a renal ultrasound scan is arranged for them.

Risk Factors For CKD, And Definition of Progression

The major risk factors for CKD are hypertension and hyperglycemia; however, other risk factors exist, including older age, certain racial/ethnic minorities, and lifestyle factors such as smoking and obesity.

- The following are recognised risk factors for progression in chronic kidney disease and most are potentially modifiable:
    - cardiovascular disease
    - proteinuria
    - acute kidney injury
    - hypertension
    - smoking
    - African, African-Caribbean or Asian family origin
    - chronic use of NSAIDs
    - untreated urinary outflow tract obstruction

- <u>Define accelerated progression of CKD as</u>:
    - a sustained decrease in GFR of 25% or more and a change in GFR category within 12months **or**
    - a sustained decrease in GFR of 15ml/min/1.73m^2 per year
- Take the following steps to identify the rate of progression of CKD:
    - obtain a minimum of 3 GFR estimations over a period of not less than 90days
    - in people with a new finding of reduced GFR, repeat the GFR within 2 weeks to exclude causes of acute deterioration of GFR — for example,

acute kidney injury or starting renin–angiotensin system antagonist therapy

- Be aware that people with CKD are at increased risk of progression to end-stage kidney disease if they have either of the following:
  - a sustained decrease in GFR of 25% or more over 12months **or**
  - a sustained decrease in GFR of 15ml/min/1.73m^2 or more over 12months
- When assessing CKD progression, extrapolate the current rate of decline of GFR and take this into account when planning intervention strategies, particularly if it suggests that the person might need renal replacement therapy in their lifetime

- In people with CKD, the chronic use of NSAIDs may be associated with progression, acute use is associated with a reversible decrease in GFR, and in some patients, can also cause acute glomerular disease and/or tubular injury. Avoid treating people with CKD with NSAIDs.

Acute kidney injury and CKD

- Take cognizance of acute kidney injury as a separate entity when responding to changes in serum creatinine. If historical renal function is unknown, regard an elevated serum creatinine as an acute event until proven otherwise and assess the patient accordingly.
- Monitor people for the development or progression of CKD after acute kidney injury as in some cases, partial recovery from acute kidney injury can result in chronic kidney disease due to impaired healing resulting from interstitial fibrosis and tubular atrophy in renal parenchyma.

Management of Diabetic Kidney Disease

Self-management

- Ensure that systems are in place to:
  - inform people with CKD of their diagnosis
  - enable people with CKD to share in decision-making about their care
  - support self-management (this includes providing information about blood pressure, smoking cessation, exercise, diet and medicines) and enable people to make informed choices
- Give people access to their medical data (including diagnosis, comorbidities, test results, treatments and correspondence) through information systems, such as Renal PatientView, to encourage and help them to self-manage their CKD

Lifestyle advice

- Encourage people with CKD to take exercise, achieve a healthy weight and stop smoking.

Dietary interventions

- Dietary advice about sodium and potassium restriction relevant to the management of hypertension or hyperkalaemia is appropriate in primary care.
- Further dietary intervention under specialist supervision may be undertaken in advanced renal disease relevant to the needs ot the patient.

Referral criteria for Nephrology Specialist Assessment

  - GFR less than 30ml/min/1.73m^2 (GFR category G4 or G5)
  - sustained decrease in GFR of 25% or more, and a change in GFR category or sustained decrease in GFR of 15ml/min/1.73m^2 or more within 12months
  - hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses (consult Hypertension [NICE clinical guideline 127])
  - known or suspected rare / genetic causes of CKD.
  - suspected renal artery stenosis
- Discussion by correspondence: In certain cases, value is best added by specialist clinics after initial discussion with the referral primary care physician in patients with an:
  - ACR 30mg/mmol or more (ACR category A3), together with haematuria: For discussion by correspondence
  - ACR> 70mg/mmol when GFR >45ml/min/m2 (with no evidence of renal progression in terms of change in eGFR): For discussion by correspondence
- Consider discussing management issues with a specialist by letter, email or telephone for above and other cases where it may not be necessary for the person with CKD to be seen by the specialist.
- People with CKD and renal outflow obstruction should normally be referred to urological services, unless urgent medical intervention is required – for example, for the treatment of hyperkalaemia, severe uraemia, acidosis or fluid overload. For patients with isolated microscopic haematuria, please refer to guidelines for referral for urological assessment.
- Suggested aspects of relevant clinical information required at referral to renal services:

  • Past medical, drug history, historical renal function and any significant recent clinical events.
  • Blood pressure
  • ACR results
  • FBC, bicarbonate, calcium, phosphate, albumin
  • Renal ultrasound (if performed)
  • Retinopathy Screening

Risk Factor Management in Chronic Kidney Disease

- Smoking cessation advice
- Weight and exercise advice
- Blood Glucose Control, HbA1c <53 mmol/mol
- Blood Pressure Targets: <140/80 mmHg if ACR <70 (PCR <100)
  <130/80 if ACR>70 (PCR >100)
  Use maximal tolerated doses of ACEi or ARB
- Dyslipidaemia - treat to guidelines

Management of individual with Diabetic nephropathy	Starting ACE inhibitor or ARB therapy
- Tight Blood Glucose control aim for targe HbA1c 48 - 53mmol/mol (6.5% - 7% (individualisation of targets is recommende in partnership with the patient) • Maintain blood pressure below 130/80mmHg - ACE inhibitors or Angiotensin II receptor blockers (ARB's) are recommended first lin drugs (unless contraindicated) - Calcium channel blocker (non-dihydropyridine class) drugs and low dose thiazide diuretics are useful second line agents - Loop diuretics are useful in the presence o volume overload - Additional anti-hypertensive therapy may be required • Treat dyslipidaemia (serum cholesterol, LDL cholesterol treated to targets) • Lifestyle changes, weight loss and smoking cessation should be advised • Patient education is an integral part of overall management	Caution in individuals with impaired kidney function • Assess kidney function and electrolytes 1-2 weeks after initiating therapy, watch out for hyperkalaemia • Assess kidney function after any subsequent increase in dose • Small rise in creatinine or a mild fall in eGFR values is expected with therapy • STOP therapy - If serum creatinine rises by >30% or >25% fall in estimated GFR seek specialist advice (to exclude possible renovascular disease) • Check renal function and electrolytes 1-2 weeks after starting/dose change • If potassium >6mmol/l and not on Spironolactone, stop ACEi or ARB. Consider arranging low potassium diet and re-instituting ACEi or ARB once potassium normalised

- Discuss the significance of a finding of abnormal albumin excretion rate, and its trend over time, with the individual concerned
- Start ACE inhibitors with the usual precautions and titrate to full dose in all individuals with confirmed raised ACR
- Have an informed discussion before starting an ACE inhibitor in a woman for whom there is a possibility of pregnancy, assessing the relative risks and benefits of the use of the ACE inhibitor

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- Substitute an angiotensin II-receptor antagonist for an ACE inhibitor for a person with an abnormal ACR if an ACE inhibitor is poorly tolerated
- For a person with an abnormal ACR, maintain blood pressure below 130/80 mmHg
- Reduce associated CVD risk: lipid control, smoking cessation, consider ASA

Pharmacotherapy

Blood pressure control

In people with CKD and diabetes, and also in people with an ACR of 70mg/mmol or more, aim to keep the systolic blood pressure below 130mmHg (target range 120–129mmHg) and the diastolic blood pressure below 80mmHg.

Choice of antihypertensive agent

    - Offer a low-cost renin–angiotensin system antagonist to people with an ACR of 3mg/mmol or more (ACR category A2 or A3)
- Do not offer a combination of renin–angiotensin system antagonists to people with CKD
- To improve concordance, inform people who are prescribed renin–angiotensin system antagonists about the importance of:
    - achieving the optimal tolerated dose of renin–angiotensin system antagonists **and**
    - monitoring eGFR and serum potassium in achieving this safely
- In people with CKD, measure serum potassium concentrations and estimate the GFR before starting renin–angiotensin system antagonists. Repeat these measurements between 1 and 2weeks after starting renin–angiotensin system antagonists and after each dose increase
- Do not routinely offer a renin–angiotensin system antagonist to people with CKD if their pretreatment serum potassium concentration is greater than 5.0mmol/litre
- When hyperkalaemia precludes use of renin–angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia (eg. glycaemia) should be undertaken and the serum potassium concentration rechecked
- Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of renin–angiotensin system antagonists, but be aware that more frequent monitoring of serum potassium concentration may be required
- Stop renin–angiotensin system antagonists if the serum potassium concentration increases to 6.0mmol/litre or more and other drugs known to promote hyperkalaemia have been discontinued.
- Following the introduction or dose increase of renin–angiotensin system antagonists, do not modify the dose if either the GFR decrease from pretreatment baseline is less than 25% or the serum creatinine increase from baseline is less than 30%
- If there is a decrease in eGFR or increase in serum creatinine after starting or increasing the dose of renin–angiotensin system antagonists, but it is less

than 25% (eGFR) or 30% (serum creatinine) of baseline, repeat the test in 1–2weeks. Do not modify the renin–angiotensin system antagonist dose if the change in eGFR is less than 25% or the change in serum creatinine is less than 30%.

- If the eGFR change is 25% or more, or the change in serum creatinine is 30% or more:
    - investigate other causes of a deterioration in renal function, such as volume depletion or concurrent medication (for example, NSAIDs).
    - if no other cause for the deterioration in renal function is found, stop the renin–angiotensin system antagonist or reduce the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if required.

Lipid Lowering Therapy

- Follow the recommendations in Lipid modification (NICE clinical guideline 181) for the use of statins in CKD and Swindon Lipid Management in Primary Care Guideline http://www.swindondiabetes.co.uk/wp-content/uploads/2015/09/Management-of-Lipids-in-Primary-Care.pdf .

Oral antiplatelet agents and anticoagulants

- Offer antiplatelet drugs to people with CKD for the secondary prevention of cardiovascular disease, but be aware of the increased risk of bleeding
- Treat non-valvular atrial fibrillation in line with existing guidelines after taking cognizance of licensing and dosing recommendations for novel oral anticoagulants with respect to renal function.

Glycaemic Management

- Aim to achieve euglycaemia individualised to the patient using detailed guidance on management or oral agents or insulin as set out in detailed accompanying guidelines. Cognizance needs to be taken on dosing guidance relevant to renal function as summarised in Table 3. Doses need to be reviewed on a continuous basis with with contemporaneous renal function.

Table 2: Anti-diabetes therapies in patients with chronic kidney disease

	Renal function					
	CKD stage 1 >90mL/min	**CKD stage 2** 60-90mL/min	**CKD stage 3a** 45-59mL/min	**CKD stage 3b** 30-44mL/min	**CKD stage 4** 15-29mL/min	**CKD stage 5** <15mL/min
Metformin	✓	✓	✓	✓ (review regularly)	✗	✗
Gliclazide	✓	✓	✓	✓	✓ (use lowest effective dose)	✗
Repaglinide	✓	✓	✓	✓	✓ (use lowest effective dose)	✓ (use lowest effective dose)
Sitaglitpin	**100mg**	**100mg**	**50mg**	**50mg**	**25mg**	**25mg**
Saxagliptin	**5mg**	**5mg**	**2.5mg**	**2.5mg**	✗	✗
Alogliptin	**25mg**	**25mg**	**12.5mg**	**12.5mg**	**6.25mg**	**?**
Linagliptin	✓	✓	✓	✓	✓	✓
Vildagliptin	**50mg bd**	**50mg bd**	**50mg od**	**50mg od**	**50mg od**	**?**
Pioglitazone	✓	✓	✓	✓	✓	✓ (monitor carefully with dialysis)
Empagliflozin	✓	✓	✗	✗	✗	✗
Dapagliflozin	✓	✓	✗	✗	✗	✗
Canagliflozin	✓	✓	✗	✗	✗	✗
Lixisenatide	✓	✓	✓	✓✗	✗	✗
Dulaglutide	✓	✓	✓	✓	✗	✗
Liraglutide	✓	✓	✓	✓	✗	✗
Exenatide	✓	✓	✗	✗	✗	✗
Insulin	✓	✓	✓	✓	✓ (requirement may be reduced)	✓

References:

1. Chronic kidney disease in adults: assessment and management. Clinical guideline [CG182] Published date: July 2014 Last updated: January 2015

2. American Diabetes Association Standards of Medical Care in Diabetesd2016 January 2016 Volume 39, Supplement 1. American Diabetes Association

3. Hypertension [NICE clinical guideline 127])
4. Lipid modification (NICE clinical guideline 181)