Managing diabetes patients with potential renal disease

Background

The Diabetes National Service Framework1 Standards 10, 11 and 12 (complications-early diagnosis, management of complications and integrated health and social care) apply particularly to renal diabetes patients. The Renal National Service Framework2 makes the measurement of estimated glomerular filtration rate (eGFR) mandatory in order that patients with chronic kidney disease (CKD) may be stratified thus:

CKD stage		eGFR (ml/min/1.73m^2)	
1*	Normal	90	*CKD stage 1 and 2 are only considered abnormal in the presence of additional evidence of renal disease; eGFR of ≥60ml/min/1.73^2 is otherwise considered normal.
2*	Mild	60-89	
3a	Mild to moderate	45-59	
3b	Moderate to sever	30-44	
4	Severe	15-29	
5	Est. renal failure	<15	

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1. Recommendations for screening in diabetes

Annual assessment of:

- urinary albumin:creatinine ratio (ACR) for microalbuminuria
- serum creatinine and eGFR (eGFR based on EPI equation)
- classification of future risk of renal disease based on
    1. **Low risk** = no microalbuminuria **and** normal eGFR
    2. **High risk** = microalbuminuria **or** overt proteinuria **or** reduced eGFR

2. Definition of microalbuminuria and overt proteinuria

	Normal	Micoralbuminuria*	Overt proteinuria
Albumin:creatinine ratio (ACR) (mg/mmol)	≤3.0	>3.0	>30
Equivalent albumin excretion rate (mg/day)	≤30	30-300	>300

***a diagnosis of microalbuminuria needs to be based on 2 out of 3 positive first passed morning urine samples (or after a period of recumbency) in the absence of a urinary tract infection**. Repeated samples need to be taken within 1 month where possible.

Microalbuminuria is the earliest indicator of renal disease (nephropathy) attributable to diabetes. Microalbuminuria relates to a range of albumin values in the urine that, while low, are above normal levels. Overt proteinuria ('macroproteinuria') relates to a more extreme increase in the levels of albumin in the urine. Occasionally, overt proteinuria may indicate renal disease which is not diabetes-related (particularly in the absence of diabetic retinopathy) and this requires a specialist renal referral (see below).

3. Early management of high-risk patients

Optimise BP (**see attached chart**). First-line choice[3] for renal preservation (in the absence of bilateral renovascular disease) with monitoring of renal function either -

- angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB)
- monitor renal function 7-10 days after initiating therapy, and after any upward dose adjustment and after any acute illness
- If serum creatinine rises by more than 30%, reduction in eGFR by 25% of baseline value, repeated measurements show progressive increases or increase in serum potassium above 6mmol/l, STOP ACEI/ARB[5]

4. Criteria for specialist nephrological referral

- Worsening proteinuria or declining renal function despite appropriate management
- Nephrotic range proteinuria (urinary ACR >210mg/mmol or urinary PCR >300mg.mmol)
- Suspicion of other renal disease i.e.nephropathy without proteinuria e.g. vasculitic rash present
- Resistant hypertension (standard BHS definition)
- CKD 3 AND decline in eGFR >2ml/min/year
- Chronic Kidney Disease stage 4 or 5 particularly for the management of renal anaemia and future care planning for managing decline in renal function (i.e. conservative management vs. dialysis)
- positive urine sediment – non visible blood and proteinuria

Unexplained haematuria should be managed according to NICE guidance https://cks.nice.org.uk/urological-cancers-recognition-and-referral#!scenario (Nov 2015)

5. When should Metformin be discontinued in those diabetes patients with renal dysfunction?

eGFR(ml/min/1.73m^2)	CKD stage	Metformin
≥90	1	Continue
60-89	2	
45-59	3a	Continue
45-30	3b	Reduce dose to maximum 1gram daily
15-29	4	Relative contraindication*
<15	5	Absolute contraindication

***** There are instances when continuing Metformin in a situation where it is relatively contraindicated (***CKD 4***) may be in the patient's best interests with dose reduction to maximum of 500mg daily. In this situation, refer for a **specialist diabetologist opinion**.

6. Summary of antidiabetic agent in CKD[7]

Drug	Stage 1CKD (GFR≥90)	Stage 2 eGFR (60-90)	Stage 3a eGFR (45-59)	3b eGFR (44-30)	Stage 4 eGFR (29-15)	Stage 5 eGFR less than15	Comments
Metformin	Continue	Continue	Continue	Continue(need to reduce dose to 1gm daily)	Relative contraindication, only under specialist advise with dose reduction to 500 mg daily	Avoid	
Gliclazide	Continue	Continue	Continue	Continue	Dose reduction might be needed	Dose reduction	Advise Frequent monitoring of CBG to avoid hypoglycaemia
Sitagliptin	Continue	Continue	Reduce to 50mg OD if eGFR less than 50	Reduce to 50mg	Reduce to 25mg	Reduce to 25mg	Generally safe in CKD but need dose reduction
Saxagliptin	Continue	Continue	Reduce dose to 2.5 if eGFR less than 50	Reduce dose to 2.5mg	Reduce dose to 2.5mg	Reduce dose to 2.5mg	Generally safe in CKD but need dose reduction
Linagliptin	Continue	Continue	Continue	Continue	Continue	Continue	No dose adjustment.
Pioglitazone	Continue	Continue	Continue	Continue	Continue	Continue	No dose adjustment. Be aware of side effect of fluid retention
Lixisenatide	Continue	Continue	Caution if eGFR less than 50	Caution if EGFR less than 50	Avoid	Avoid	
Exenatide	Continue	Continue	Caution if eGFR less than 50 (for standard release)	Avoid	Avoid	Avoid	Avoid if eGFR less than 50 with modified release
Liraglutide	Continue	Continue	Continue	Continue	Dose reduction might be needed	Off licence, under specialist advise	
Dulaglutide	Continue	Continue	Reduce to 5mg	Avoid	Avoid	Avoid	
Semaglutide (12)	Continue	Continue	Continue	Continue	Avoid	Avoid	
Dapagliflozin	Continue	Continue	Continue	Avoid	Avoid	Avoid	
Empagliflozin	Continue	Continue	Reduce to 10 mg	Avoid	Avoid	Avoid	
Canagliflozin	Continue	Continue	Reduce to 100mg	Avoid	Avoid	Avoid	
Insulin							Dose reduction might be needed

7. Sick day guidance [7]

- The patient should stop taking the medications listed if they are unwell with recurrent vomiting, diarrhoea or having febrile illness.
- The medication can be restarted 24-48 hour after starting eating and drinking.
- The medications are; metformin, SGLt2, ACEi, ARBs, NSAIDs and diuretics.

8. Glucose flash monitoring [9]

Insulin dependent diabetic patients with CKS stage 5 on dialysis could be considered for flash glucose monitoring Libre under specialist advice.

9. Target glycaemic control

HbA1c can be overestimated in the setting of increased blood urea, uraemia (increased glycosylation rate), iron deficiency (common in haemodialysis). Factors that cause falsely low HbA1c in CKD ; need for repeated blood transfusions; and use of erythropoietin (higher proportion of younger red blood cells) [10]. In such circumstances self-monitoring of capillary blood glucose would be would be more accurate.

	CKD stage	**HBA1C target**
Type 1 diabetes	• Young people within 10 years duration of diabetes • CKD stage 1-2	48-58 mmol/mol
	• CKD stage 3-4	58-62 mmol/mol
	• Stage 5	58-68 mmol/mol
Type 2 diabetes	• CKD stage 1-2	48-58 mmol/mol
	• CKD stage 3-4 on oral hypoglycaemic, GLP-1 agonist or insulin • CKD stage5	58-62 mmol/mol

	CKD1	CKD2	CKD3	CKD4	CKD5
No albuminuria	No action if BP<140/80	No action if BP<140/80	Action required ∞ BP<140/80	Action required Refer nephrology ∞♦	Action required Refer nephrology ∞♦
Microalbuminuria*	**BP<130/80**	**BP<130/80**	**BP<130/80∞**	Action required Refer nephrology ∞♦	Action required Refer nephrology ∞♦
Dip +ve proteinuria*	**BP<130/80**	**BP<130/80**	**BP<130/80∞**	Consider referral to nephrology ∞♦	Consider referral to nephrology ∞♦

For all patients with diabetes, aim for:	∞ ***CKD 3/4/5***	♦ ***CKD 4/5***
Target HBA1c in the absence of hypoglycaemia. Frail elderly patients with multiple comorbidities will aim for looser targets (58-70mmol/mol)	**PTH[a]**	**There may be instances when it is inappropriate to refer patients to the nephrologist e.g. because of severe co-morbidity** **Where renal replacement therapy would not be considered in the patient's best interests.** **In any doubt, please speak to the nephrologists about referral criteria.**
No Smoking	**Haemoglobin[b]**	
Lipids local guidance on HERPC website (see link below) When eGFR <60ml/min use atorvastatin 20mg ; CKD 4/5 only adjust dose with nephrology guidance.	**Serum ferritin & transferrin saturation[c] if Hb<11g/l**	
Attain healthy BMI or reduction in waist circumference	**Renal USS if lower urinary tract symptoms**	
Immunise pneumococcus/flu. Drug review (e.g. NSAID use)		
For all 'high risk' patients (i.e. microalbuminuria+ or urine dip + protein) use ACEI or ARB ***Lipids: http://www.hey.nhs.uk/wp/wp-content/uploads/2016/03/lipidPrescribingFullGuidance.pdf***		

10. All tests advised on an annual basis

[a] PTH ***3 times the upper limit of normal***, then repeat. If PTH ***raised 3 times upper limit of normal on 2 occasions (minimum 3 months apart) refer NEPHROLOGY.***

[b] **Hb<11g/l**, exclude causes other than chronic renal disease

[c] **ferritin/transferrin saturation guidance:**

Hb (g/l)	Serum ferritin (mg/dL)	OR Serum transferrin saturation	Action	Comment
>110	Not required	Not required	Monitor annual Hb	-
≤110	<200	<20	Iron supplement for 3/12	Repeat Hb and serum ferritin after oral iron replacement
≤110	Remains <200 after oral iron replacement	<20	Refer nephrologist	IV iron infusion may benefit patient
≤110	≥200	≥20	Refer nephrology if patient symptomatic of anaemia	Patient may benefit from Erythropoietic stimulating agent (ESA) treatment

Note: [(11)] -use a combination of transferrin saturation and serum ferritin measurement to diagnose iron deficiency anaemia
-Alternative tests are hypochromic red blood cells (% HRC; more than 6%) or reticulocyte haemoglobin (Hb) content (CHr; less than 29 pg).
- hypochromic red blood cells (%HRC) sample need to be processed within 6 hours

11. Hepatitis B vaccination [8]

Indicated for the active immunisation of individuals who are 15 years of age or over and are on haemodialysis, a renal transplantation programme or have chronic renal failure (CKD stage 4 or 5) that is likely to require haemodialysis or transplant

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